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REVIEW

Chemotherapy for Metastatic Bladder Cancer. Is there New Hope?

J. WAXMAN

Department of Clinical Oncology, Royal Postgraduate Medical School, Hammersmith Hospital, London

Urothelial cancer is common in the United Kingdom and each year approximately 6900 men and women are registered (Cancer Statistics, 1988) with the disease and 4700 die (Mortality Statistics, 1988) as a result. The outlook for the patient with metastatic urothelial cancer is very poor and the median duration of survival for untreated patients is approximately 3 months. Placing this life expectancy in context, it should be noted that metastatic urothelial cancer has a worse prognosis than lung cancer or acute leukaemia. Urologists are aware of the need to improve upon the grim outlook for patients with this condition and in collaboration with oncologists and radiotherapists have organised a systematic approach to the investigation of new treatment programmes. In the last 5 years there have been changes in our management of metastatic urothelial cancer and these changes have come from investigational chemotherapy programmes.

There is no doubt that urothelial cancer is responsive to chemotherapy. The order of response to a wide range of single agent treatments is high, much higher than response rates in other common solid tumour groups such as colorectal cancer. In oncology, where there is a high order of response to single agents, the expectation is for an even higher response rate when these agents are combined. Applying the same sort of logic to bladder cancer as has been applied to the successful treatment of testicular cancer, it is not unreasonable to hope for the attainment of the Holy Grail of the right combination chemotherapy programme and the cure of bladder cancer. There may be problems associated with the use of combination chemotherapy due to additive effects in terms of toxicity. This may be acceptable in young patients who are reasonably fit and have good marrow reserves, but the average age of patients with metastatic bladder cancer is 70 years, and investigational chemotherapy programmes need careful assessment with regard to treatment-related morbidity and mortality.

Analysis of the results of clinical trials is dogged by the difficulty of making a true comparison between studies. Even if there is not observer bias in the enthusiastic early reporting or interpretation of results, there is editorial bias in that only successful trials are published. Typically, a study of combination chemotherapy will describe response rates in approximately 50 patients without reference to a control group. Such study numbers will estimate the response rate to within 15% of the true rate of response. Thus an extension of the study to include a larger number of patients might lead to a true response rate of 35%, a result not much better than that expected for single agent treatment. The publication of follow-up reports may not proceed because of poorer results and so great care needs to be taken in the interpretation of the early results of clinical trials in small groups of patients.

Single Agent Chemotherapy

An extraordinary variety of cytotoxic agents are effective in the treatment of bladder cancer. These include intercalating agents such as doxorubicin (Adriamycin), drugs having an effect on the cell spindle such as the vinca alkaloids, alkylating agents such as 5-fluorouracil and cyclophosphamide and antimetabolites including methotrexate (Table 1). Analysis of the results of investigational pro-

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Table 1 Single Agent Chemotherapy For Urothelial Cancer

	No. CR+ PR/No. entered	*%CR +PR*	*95% Confidence (%)*
Cisplatin	90/320	30	(25–35)
Methotrexate	68/236	29	(23–35)
Doxorubicin	47/274	17	(13–22)
Vinblastine	6/38	16	(4–28)
Vincristine	3/31	10	(2–26)
Cyclophosphamide	30/98	31	(22–40)
5-Fluorouracil	22/131	17	(11–25)
Mitomycin-C	5/42	13	(2–22)
VP-16	3/49	6	(0–13)
Gallium nitrate	5/16	31	(9–54)
Bleomycin	6/102	6	(1–10)
AMSA	6/60	10	(2–18)
Carboplatin	4/7	60	(2–94)
10-Deaza-aminopterin	3/15	20	(0–40)
Neocarcinostatin	1/19	5	(0–15)

(Scher and Sternberg, 1985).

grammes is difficult because mixed patient populations are usually treated. Response rates and durations in locally advanced cancer and metastatic disease differ, but both groups are generally considered when describing the efficacy of treatment.

Antimetabolites

Methotrexate was the first agent to be used in the management of bladder cancer and its use dates back to the early 1960s. It acts by inhibiting folate metabolism and so limits nucleic acid synthesis. Many different schedules of administration of this agent have been used, including oral, intramuscular and intravenous routes, weekly or fortnightly, with or without folinic acid rescue. The most commonly applied schedule involves a starting dose of 50 mg weekly IV, increasing gradually by 25-mg increments to 100 mg or toxicity. Clinicians have tried to discover whether or not there is a dose response relationship for methotrexate. This has not been satisfactorily established. The side effects of methotrexate include mucositis and, more rarely, conjunctivitis, but these can be avoided if care is taken to moderate dosage in the presence of compromised renal function, pleural effusion, ascites, or an ileal conduit which leads to delayed clearance or methotrexate reabsorption. These side effects may be moderated by reducing the dosage or providing folinic acid rescue. Responses are seen in approximately 30% of patients for a median duration of approximately 6 months (Turner *et al*, 1977; Oliver *et al.*, 1983).

Cisplatin and platinum analogues

Cisplatin is one of the most active agents in the treatment of bladder cancer. Cisplatin and its analogues bind to DNA to form large molecular weight complexes at guanine rich sites. This adduct results in the inhibition of DNA polymerase activity. Patients are generally treated with doses of 50 to 120 mg/m^2 every 3 to 4 weeks. There seems to be no difference between response rates using different dosages within this range and the most commonly chosen regimen is 70 mg/m^2, 3-weekly. The response rate is 30 to 40%, approximately that achieved by methotrexate. Unfortunately, like methotrexate, the median duration of response is short (4–6 months), with very few long-term responses (Yagoda *et al.*, 1976; Soloway, 1978). The toxic effects of cisplatin include severe vomiting, impairment of renal function and eighth nerve damage. New platinum analogues have been designed to reproduce the efficacy of cisplatin without its toxicity. Carboplatin has emerged as one of the most successful of these compounds and its use is associated with less acute toxicity and no renal or eighth nerve impairment. There have been a number of studies on the effect of carboplatin given as a single agent in bladder cancer and the conclusions are controversial, some studies showing benefit (Craven, 1984) and others no activity in the disease (Medical Research Council, 1987). These studies are of small numbers of patients and carboplatin requires further evaluation in bladder cancer because of the potential advantages to patients resulting from its limited toxicity.

Anthracyclines

Anthracyclines exert a therapeutic effect by generating free radicals within cells which result in the destruction of DNA. Doxorubicin is effective in bladder cancer but is less active than methotrexate or platinum compounds. It is given as a single agent in dosages of 30 to 75 mg/m^2 at 3-weekly intervals and responses are seen in approximately 15% of the patients treated for a median duration of 3 to 5 months (Carter and Wasserman, 1975; Merrin *et al.*, 1975). Doxorubicin's side effects are dose-dependent and include vomiting, hair loss, cardiac damage and marrow suppression. The duration of response is similar to that achieved by methotrexate and platinum analogues. Mitozantrone has been investigated as an alternative anthracycline therapy. Its advantages are that it has less acute toxicity and, dose for dose, much less cardiotoxicity than doxorubicin. Investigation of mitozantrone as a single agent is limited and there is a single report of its lack of effect in 28 patients (Van Oosterom *et al.*, 1985). Because of its apparently limited toxicity, epirubicin is under investigation in bladder cancer as an alternative to doxorubicin.

Vinca Alkaloids

Vinca alkaloids inhibit the synthesis of the cell mitotic spindle by binding tubulin, a protein that polymerises to form the cell spindle. Vincristine seems to be less effective than vinblastine in the treatment of bladder cancer (Richards *et al.*, 1983). As a single agent, vinblastine is given at a dosage of approximately 5 mg/m^2 weekly and response is seen in approximately 15% of patients for up to 5 months (Blumenreich *et al.*, 1982). There is little acute toxicity with this single agent and its main side effects are on the bone marrow.

Alkylating agents

Alkylating agents act by cross linking strands of DNA. Among the alkylating agents used in bladder cancer, cyclophosphamide seems to be the most active and in a variety of dose schedules has a response rate of approximately 30%. The duration of response is approximately 4 to 6 months. Given at a dosage of 1 g/m^2 every 3 weeks, 11 of 21 patients with localised or metastatic cancer responded for an average period of 9 months (Merrin *et al.*, 1975). Cyclophosphamide in the dosages used for the treatment of bladder cancer has only limited toxicity, but may lead to chemical cystitis and marrow suppression.

Other single agents

Various agents, including m-AMSA, bleomycin, the nitrosoureas and the podophyllotoxins, VP-16 and VM-26, have been used as single agents in patients with bladder cancer. Their activity is significantly less than that of the agents described above and is probably less than 10%.

Combination Chemotherapy

The aim of combination chemotherapy for bladder cancer is to improve upon the results of single agent treatment in terms of initial response rate and its duration. As has been demonstrated, a large number of single agents seem to be active in bladder cancer. Given the order of activity of single agents, it should be possible to produce combinations of drugs that are more effective than single agents. However, combining chemotherapeutic agents generally results in increased toxicity and since patients with bladder cancer tend to be elderly, their frailty requires care in the design of combination chemotherapy programmes with due consideration for the quality of their lives.

Cisplatin and cyclophosphamide

This combination has been investigated in patients with metastatic disease and response rates are similar to those obtained with single agent therapy. A dosage of 70 mg/m^2 cisplatin and 250 to 1000 mg/m^2 cyclophosphamide given every 3 weeks produced responses in 15 of 35 patients (Yagoda *et al.*, 1976) and in 7 of 59 patients treated with cisplatin 70 mg/m^2 and cyclophosphamide 750 mg/m^2 (Soloway *et al.*, 1983). Toxic effects included nausea and vomiting, with additional haematological toxicity, nephrotoxicity and cystitis. In these studies the median duration of response was approximately 10 months.

Cisplatin and doxorubicin

Doxorubicin 50 mg/m^2 given with cisplatin 50 mg/m^2 at 3-weekly intervals led to responses in 16 of 37 patients compared with 8 of 41 responses in patients who were randomised to treatment with doxorubicin 50 mg/m^2 alone (Gagliano *et al.*, 1983).

Cisplatin and Methotrexate

Cisplatin 70 mg/m^2 given on day 1 and methotrexate 40 mg/m^2 on days 8 and 15 of a 3-weekly treatment cycle were given to 43 evaluable patients; 10 showed a complete response and 10 a partial response. The median duration of complete response was 64 weeks. Toxicity included leukopenia and neutropenic sepsis together with nausea, vomiting and mucositis. Only 17% of the patients received treatment exactly according to the protocol because of these side effects (Stoter *et al.*, 1987).

Cisplatin, doxorubicin and cyclophosphamide

Combination chemotherapy with cisplatin, doxorubicin and cyclophosphamide (CAP) has been extensively investigated. Dosages range from 40 to 75 mg/m^2 for cisplatin, with doxorubicin at 50 mg/m^2 and cyclophosphamide at 250 to 500 mg/m^2. Three complete and 10 partial responses were seen in 34 patients for a median duration of 25 weeks (Troner and Hemstreet, 1981), and 2 complete and 11 partial responses in 32 patients for a median duration of 32 weeks (Schwartz *et al.*, 1983). In 42 patients treated in the EORTC study 30771, 5 complete and 12 partial responses were reported, of median duration 5 to 7 months (Newling *et al.*, 1987). CAP chemotherapy has been investigated in randomised trials. m-AMSA has been compared with this regimen by the South West Oncology Group. Ten of 23 patients responded to CAP for a median duration of 28 weeks and 4 of 22 patients to m-AMSA for a median duration of 21 weeks (Al-Sarraf *et al.*, 1985). In a randomised, prospective study, cisplatin alone was compared with CAP therapy. Seven of 45 patients responded to single agent and 9 of 42 patients to combination therapy. The median duration of response to both treatments was 12 weeks and there were 2 deaths that were thought to be treatment-related (Troner *et al.*, 1987). In all of these studies the data are difficult to interpret because mixed groups were treated, including patients with disease in the bladder alone and patients with metastatic cancer. Treatment with this combination is complicated by nausea, vomiting, marrow and renal toxicity and death.

Vinblastine and methotrexate

Vinblastine 3 to 4 mg/m^2 and methotrexate 30 to 40 mg/m^2 were given to 57 patients with metastatic bladder cancer; 19 had a complete or partial response for a median duration of 8 months. Patients with poor prognosis cancer, including those with CNS metastases, responded to chemotherapy. Side effects included mucositis and neurotoxicity without significant haematological toxicity (Ahmed *et al.*, 1985).

Cisplatin, methotrexate and vinblastine (CMV)

This programme was initiated by the Northern California Oncology Group in 1982. Treatment consists of methotrexate 30 mg/m^2 and vinblastine 4 mg/m^2 on day 1 and cisplatin 100 mg/m^2 on day 2 of a 3 to 4-week treatment cycle. Initial reports describe response rates in 50 patients; 14 had a complete response (28%) and 14 a partial response. The median duration of response was 5 months. Complications included neutropenic sepsis and nephrotoxicity with septic death (Myers *et al.* 1985).

Methotrexate, vinblastine, doxorubicin and cyclophosphamide (M-VAC)

M-VAC chemotherapy was developed at the Memorial Sloan-Kettering Cancer Center in New York City and was based on considerable experience with single agent treatment and combination chemotherapy. The most effective single agents were combined to produce the M-VAC programme. This consists of methotrexate, vinblastine, doxorubicin and cisplatin given as shown in Table 2.

Table 2 M-VAC (mg/m^2)

Agent	*Day* *1*	*2*	*15*	*22*
Methotrexate	30		30	30
Vinblastine		3	3	3
Adriamycin (doxorubicin)		30		
Cisplatin		70		

Between 1983 and 1985, 92 patients with nodal or extranodal metastatic urothelial cancer were treated and 83 were available for assessment; 31 had a complete and 26 a partial response to chemotherapy. The median duration of complete response has not been reached but exceeds 2 years; the duration of partial response is 8 months. Toxicity was significant and 20% of the patients developed neutropenic sepsis, 31% grade 1 renal toxicity and 41% grade 1 mucositis; 4% patients died as a result of treatment. Poor sites for response were liver (9%) and bone (33%). Ten patients were converted to complete responders by surgical resection of residual disease (Sternberg *et al.*, 1988).

Methotrexate, vinblastine, mitozantrone, carboplatin (MVMJ)

In view of the considerable toxicity associated with M-VAC therapy and the apparent advantages of this regimen over all other combination chemotherapy programmes, we have adapted treatment using similar agents with apparently less toxicity. In a preliminary report, 9 complete and 12 partial responses were described in 33 patients with either poor prognosis locally advanced, or metastatic urothelial cancer treated with MVMJ (methotrexate, vinblastine, mitozantrone and carboplatin). This regimen (Table 3) was without significant toxicity (Waxman *et al.*, 1989).

Within recent years a number of programmes have appeared that seem successful in the management of bladder cancer. There is an increasing tendency to treat patients with early stage tumours

Table 3 MVMJ Chemotherapy (mg/m^2)

Agent	*Day* *1*	*15*
Methotrexate	50	50
Vinblastine	3	
Mitozantrone	10	
Carboplatin	200	

more aggressively and this is because actuarial analysis shows poor survival even in relatively early stage cancer, so that the survival rate for G3 T1 cancer is approximately 20% at 5 years. Many clinicians are now investigating the need for so-called aggressive therapy for early stage disease, employing regimens found effective in metastatic urothelial cancer. This is because patients with early stage cancer die of "aggressive" metastatic disease despite "cure" of their local bladder disease and it is felt that early stage bladder cancer should be regarded as a systemic malignancy that requires systemic therapy.

A number of prognostic factors appear to be important in the management of bladder cancer and these include atypical histology, metastases to atypical sites, age, lack of response to previous radiotherapy to the bladder and previous treatment with cytotoxic chemotherapy. Although these adverse prognostic factors do not result, in most instances, in a different approach to the patient with poor prognosis disease, they should perhaps influence our approach so that persistence with treatment does not continue in the face of advancing disease.

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Immunobiotherapy with Uro-Vaxom in Recurrent Urinary Tract Infection

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Summary—A series of 120 patients with recurrent urinary tract infection (UTI), all in acute recurrence at the start of the trial, were treated for 3 months under double-blind conditions with 1 capsule daily of either the immunobiotherapeutic product Uro-Vaxom (UV) or a placebo. They were then observed for 3 months without treatment. During the 6 months of the trial a significant decrease was noted in the UV group compared with the placebo group with respect to the number of recurrences of UTI, total consumption of antibiotics and chemotherapeutic agents, bacteriuria and dysuria. By the sixth month the UV patients were receiving no antibiotics. The final assessment was that UV was significantly more effective than the placebo. UV was well tolerated, with possible mild side effects in only 4 patients. During a further observation period of 5 months, patients who had received UV during the first period had fewer recurrences of UTI than those who had received placebo, confirming the long-term protective action of UV.

The treatment of chronic or recurrent urinary tract infection has become increasingly difficult since the emergence of antibiotic-resistant strains of organisms (Johnson, 1978). Over 50% of UTIs in young women recur within 12 months (Leski, 1983). The therapeutic value of activators of the body's immune defence mechanisms for therapy in such conditions is currently being explored (Fries, 1983). Uro-Vaxom (also known as Coli-Vaxom or OM-8930; manufactured by OM Laboratories, Meyrin, Geneva, Switzerland) is a new agent of this class which has been shown to increase the active T cell population and the proliferative responses to different mitogens (Rosenthal, 1986). It contains immunostimulating fractions extracted from *Escherichia coli* and is administered orally in a capsule. In a double-blind study involving 64 patients with recurrent UTI treated with UV for 3 months, Frey *et al.* (1986) noted a significant reduction in bacteriuria, dysuria, leucocyturia and the use of antibiotics and chemotherapeutic agents.

The aim of the present study was to investigate the frequency and severity of recurrences under double-blind conditions in a larger group of patients.

Patients and Methods

Initially, 150 patients suffering from recurrent UTI were admitted to the trial. The inclusion criteria were: acute urinary infection with at least 10^5 organisms/ml in midstream urine or 10^4 organisms/ml in catheter urine at initial examination on CLED medium (for total organisms) or MacConkey medium (for gram-negative organisms) (Uribak, Biotechnik GmbH, Hamburg, Federal Republic of Germany) and at least 2 recurrences of UTI during the 6 months preceding the trial. The exclusion criteria were: dysuria without positive bacteriological findings, indwelling catheter, pregnancy, recurrent post-coital cystitis and urinary tract abnormalities. All patients gave informed consent before entering the trial.

Patients were randomly assigned to 3 months' treatment with 1 capsule daily of either UV or a placebo. A UV capsule contained 6 mg of immunostimulating fractions from *Escherichia coli* in lyophilised form. The treatment period was fol-

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lowed by 3 months' observation without treatment. Antibiotics and chemotherapeutic agents were given as necessary throughout the trial. At the end of the 6-month trial, 57 patients (27 from the UV group and 30 from the placebo group) were kept under observation, independently of the study protocol, for about 5 months (average 24 weeks) and were given no treatment. Each patient had a medical examination at the beginning of the trial, at 3 and 6 months, 1 week after the end of initial antibiotic administration (usually about week 3) and at any possible recurrence of UTI. For the purposes of statistical analysis a recurrence was defined as the presence of bacteriuria with $\geqslant 10^4$ organisms/ml at any examination after the beginning of the trial. A record was made of concomitant treatment with antibiotics or chemotherapeutic agents, bacteriuria, dysuria, proteinuria, nitrituria, and numbers of urinary erythrocytes, leucocytes and casts, as well as patient compliance. The test products were evaluated in the light of their curative effects on the initial infection, their long-term consolidative efficacy, and their tolerance.

Of the initial 150 patients, 30 were not eligible for statistical analysis because of poor compliance (15 patients), a short observation period (1 patient), or factors related to the inclusion or exclusion criteria (14 patients). Thus 120 patients were statistically assessable: 61 of these (9 men and 52 women, mean age 51.2±2.4 years) had received UV and 59 (8 men and 51 women, mean age 50.4±2.3 years) had received placebo. Both groups were homogeneous with regard to age, sex, medical history (including number of UTI recurrences and use of antibiotics or chemotherapeutic agents) during the 6 months preceding the trial, and urinary characteristics at the beginning of the trial. All 150 patients were considered in the tolerance analysis. For comparison between treatment groups the 2-tail Student's *t* test was used for normally distributed variables, the Mann-Whitney *U* test and the Wilcoxon ranks *W* test for non-normally distributed variables and ordinal variables, and either the χ^2 test or Fisher's exact test (depending on the size of n) for frequencies. For comparison within groups the paired *t* test was used for continuous variables, the Wilcoxon test for ordinal variables, and McNemar's test for dichotomic variables.

Results

Recurrences

The mean number of recurrences, approximately 3.5 during the 6 months preceding the trial, was 0.82 in the UV group and 1.8 in the placebo group during the trial. The total number of recurrences was significantly lower in the UV group than in the placebo group, being respectively 38 and 63 ($P<0.05$) during the first 3 months, 12 and 41 ($P<0.01$) during the second 3 months (*i.e.* those without treatment) and 50 and 104 ($P<0.001$) for the total 6 months. The distribution of patients per number of recurrences was as follows (UV and placebo respectively): no recurrences (23, 10); 1 recurrence (27, 19); 2 recurrences (10, 10); 3 recurrences (1, 16); 4 recurrences (0, 3); 5 recurrences (0, 1) ($P<0.001$) (Fig. 1). In the additional follow-up study of 5 months without treatment after termination of the 6-month trial, recurrences occurred in only 10 of the 27 ex-UV patients, but in 20 of the 30 ex-placebo patients ($P<0.05$).

Antibiotics and chemotherapeutic agents

The total consumption of these products, assessed by the total number of days upon which they were administered, was approximately equal in the 2 groups during the first 3 weeks of the trial, but was significantly less in the UV than in the placebo group for the whole trial period ($P<0.001$) (Fig. 2).

The mean duration of antibiotic and chemotherapeutic use at the end of the third month (UV and placebo respectively) for antibiotics was 0.16 and 0.72 days ($P=0.08$) and for chemotherapeutic agents 0.44 and 1.02 days. At the end of the sixth

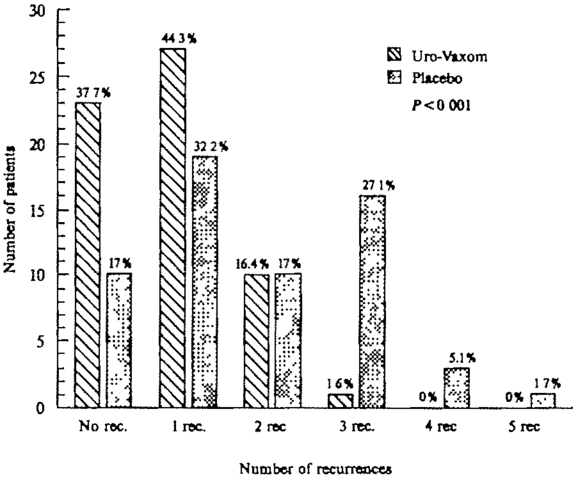

Fig. 1 Distribution of patients according to number of recurrences of infection during the 6-month trial period. A low incidence (0–1) predominated in the UV group and a higher incidence (3–5) in the placebo group.

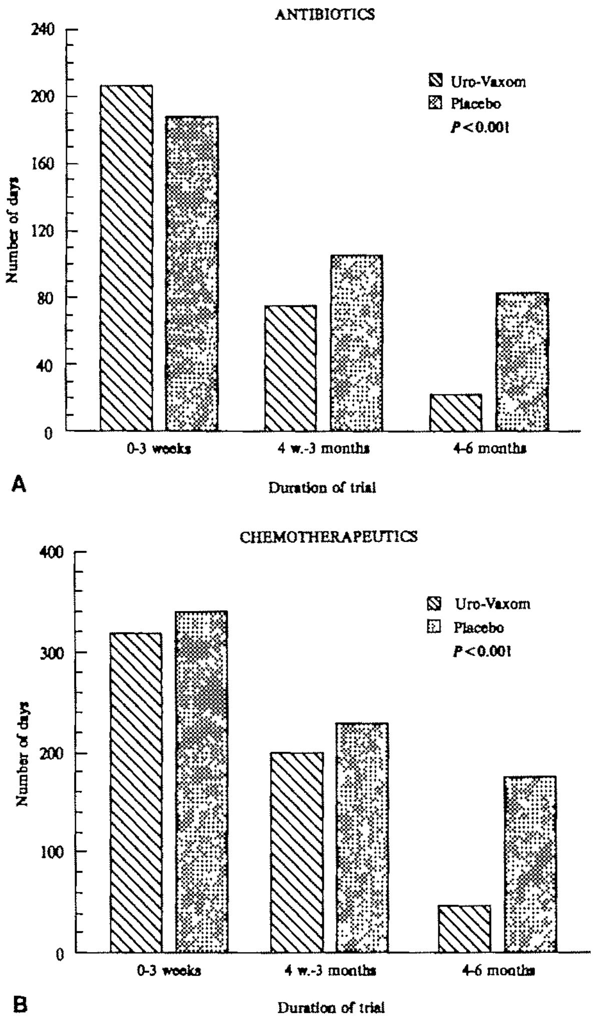

Fig. 2 Total consumption of antibiotics (A) and chemotherapeutic agents (B) expressed as number of days of adminstration during the 6-month trial period.

month it was 0 and 0.39 days (the absence of antibiotic in the UV group preventing the calculation of statistical significance) and 0.25 and 0.65 days.

Bacteriuria

Bacteriuria assessed on CLED medium (total number of organisms) was significantly less ($P<0.01$) in the UV group than in the placebo group at 3 and 6 months (Fig. 3).

Dysuria and nitrituria

At the beginning of the trial 93.4% of the UV patients and 91.5% of the placebo patients had dysuria, compared with 8.2 and 24.6% at the end of the sixth month ($P<0.05$). The corresponding figures for nitrituria were 83.6 and 86.4% and 4.9 and 15.8% ($P<0.05$).

Other urinary findings

Protein, erythrocytes, leucocytes and casts all decreased more in the UV than in the placebo patients, but the differences were not statistically significant.

Tolerance

Possible side effects were reported in 4 (5.4%) of the UV patients (pruritus, an allergic reaction leading to withdrawal of UV, diarrhoea, and headache with flushing) and in 2 (2.6%) of the placebo patients (repeated nausea, erythema).

Physicians' assessment

The efficacy of the test products with respect to their curative effect on the initial infection was judged to be "evident" in 31.1% of the UV patients and in 8.5% of the placebo patients, and to be "positive" (*i.e.* "evident" and "possible" efficacy taken together) in 95.1 and 72.9% respectively. Efficacy, in relation to long-term consolidative action assessed at 6 months, was judged as "evident" in 54.1% of the UV patients and 13.8% of the

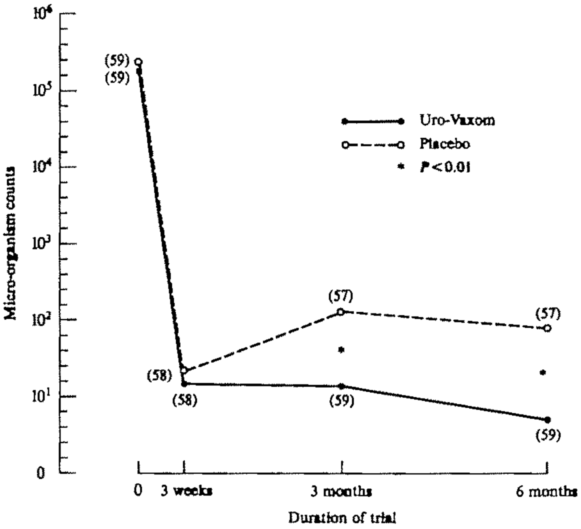

Fig. 3 Bacteriuria (CLED medium) in 118 patients (data not available for 2 patients) with urinary tract infection, half treated with Uro-Vaxom and half with placebo for 3 months and observed for a total of 6 months. Figures in parentheses are numbers of patients (2 placebo patients failed to complete the trial).

placebo patients and as "positive" in 95.1 and 60.3% respectively. The intergroup difference was highly significant ($P < 0.001$) for the assessments of both the curative and consolidative effect.

Discussion

This study has provided convincing evidence of the curative and consolidative effectiveness of UV in UTI as assessed by objective clinical criteria. Recurrences of infection, antibiotic and chemotherapeutic prescription, bacteriuria and the number of patients suffering from dysuria decreased in the UV patients in comparison with those treated by placebo.

The long-term protective action exerted by UV as a consequence of its stimulation of the body's immune system was confirmed by the significantly lower incidence of recurrences of UTI in the UV-treated patients observed without treatment for 5 months after the end of the 6-month trial, as compared with the placebo-treated patients. Thus, by consolidating the body's defences a 3-month course of UV reduces recurrences of UTI both during and after treatment.

The low incidence of side effects, even following prolonged administration, and the long-term protection against recurrence make UV a valuable complement to antibiotics, especially as the latter do not always prevent recurrent infection (Jameson, 1976; Stamm *et al.*, 1980), and may even, on repeated administration, lead to the emergence of antibiotic-resistant bacterial strains and untoward side effects (Braun *et al.*, 1981; Hannedouche *et al.*, 1983).

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The Incidence of Post-operative Urinary Tract Infection in Patients with Ureteric Stents*

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Summary—Despite the many advantages provided by the ureteric stent, it produces a foreign body reaction and increases the risk of infection. We undertook a study on the rate of infection in a group of paediatric patients with ureteric stents; 40 ureteric stents, 6 to 9 F, were used in 36 children undergoing the following procedures: 18 pyeloplasties, 20 antireflux ureteric reimplantations and 2 uretero-rectal anastomoses. Only patients with sterile urine pre-operatively were included in the study. All received antibiotic cover in the post-operative period.

Positive urine cultures were found in only 3 patients (7.5%). In spite of this low incidence, the urine specimens collected from all children 1 month after removal of the stent showed a much higher incidence of infection. It was concluded that ureteric stenting is a safe procedure with a low rate of infection provided that antibiotic cover is given.

Much controversy still exists concerning the use of stents in ureteric surgery. Davis (1958) reviewed the use of stents in the ureter, but Persky and Krause (1981) suggested that stents should be avoided when anastomotic conditions were ideal. Hamm and Weinberg (1955), Webb *et al.* (1957) and Casey (1959) obtained excellent results using only paraureteric drainage without a stent or indwelling catheter. Eckstein (1980) (unpublished observations) reported that 84% of 91 babies who received pyeloplasties, without stent or nephrostomy, had urinary extravasation and leakage from the para-renal drains for 1 to 4 weeks.

Gibson (1959) maintained that ureteric stenting was necessary in infected patients, in secondary surgery and in elderly patients. Persky *et al.* (1981) and Snyder *et al.* (1980) advised using the stent for pyeloplasties in children to prevent adhesions at the anastomotic site.

What are the advantages and disadvantages of ureteric stents? They encourage the drainage of urine in the early post-operative period, thus circumventing obstruction which may occur as a result of oedema at the anastomotic site or atonicity of the collecting system. They also limit the risk of urinary extravasation.

The disadvantages include delayed mobilisation of the patient, possible obstruction of the stent (especially if it is small), foreign body reaction and, most important, the possibility of bacterial contamination.

The aim of the present investigation was to analyse the incidence of post-operative urinary tract infection in a group of children with ureteric stents.

Patients and Methods

Studies were carried out on 36 children (20 males, 16 females; age range 1–12 years, mean 6 years 8 months) with 40 ureteric stents positioned during surgery on the ureter between 1983 and 1986. One of the conditions for entry into the study was sterile urine pre-operatively. The operations performed were 18 Anderson-Hynes pyeloplasties for congenital pelviureteric junction obstruction, 20 ureteric reimplantations using the Glenn or Cohen or

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Politano technique (17 for primary vesico-ureteric reflux, 2 for primary megaureter and 1 for ureteric ectopy) and 2 uretero-intestinal anastomoses in rectal bladder using the Heitz-Boyer Hovelaque technique. During surgery, transparent polyvinyl ureteric stents 6 to 9 F were positioned with the proximal end in the renal pelvis and the distal end brought out transurethrally (20 stents), through the bladder wall suprapubically (18 stents) and through the anus (2 stents) in the patient with a rectal bladder. The urine was drained into bags and any manipulation of the distal end of the stents was performed in sterile conditions and recorded on a chart. The ureteric stents were removed after 5 to 15 days (mean 8). Four samples of urine were studied. Urine for culture was collected from the distal end of the stent on the first and fourth days after surgery, on the day of stent removal and then 1 month after stent removal. One month after removal, urine was collected by urethral catheterisation in females and from mid-stream urine in males. All patients received antibiotic cover during the post-operative period. Cephalosporins were administered in weight-related doses, i.m. or i.v. for the first 3 to 4 days and then orally for a further 2 weeks after removal of the stent.

In 3 children a retrograde cystogram was carried out with the ureteric stent still *in situ* to establish the possible occurrence of vesicoureteric reflux due to the stent itself.

Results

Of the 40 stents studied, significant bacteriuria ($\geq 10^5$ col/ml) was observed in urine from 3 stents (7.5%); in the remaining 37, urine was sterile (Table). In 2 cases monomicrobic flora (*Escherichia coli* or *Pseudomonas aeruginosa*) were present, whilst in the third case a polymicrobic flora (*Proteus mirabilis* and *Enterococcus*) was observed. In all 3 cases, culture was positive only in the third specimen collected upon removal of the stent (8, 10 and 12 days after surgery respectively). All samples taken on the first and fourth post-operative days were therefore sterile. Urine infection in all 3 cases was observed only as a laboratory finding with no associated clinical symptoms.

The 40 stents were divided into 3 subgroups according to the duration of stenting. In the group (7 cases) in which the stents had been left for 5 to 7 days, no positive cultures were found; in the group (26 cases) in which the stents were removed after 8 to 11 days, 2 positive cases (7.6%) were observed and in the group (7 cases) in which the stents were left for 12 to 15 days, 1 positive case (14.2%) was reported. No relationship was found between positive cultures and the frequency of manipulation of the distal end of the stent during the post-operative period (flushing, bag emptying, etc).

Table Results

	No. of patients (%)
Negative urine cultures during stenting	37 (92.5)
Positive urine cultures during stenting	3 (7.5)
Negative cultures at 1 month	18 (60.0)
Positive cultures at 1 month	12 (40.0)

Of the 3 children with a positive culture, 2 had undergone pyeloplasty for PUJ obstruction and 1 had had ureteric reimplantation and tailoring for primary megaureter (11.5% of the pyeloplasties and 5% of the ureteric reimplantations).

Urine cultures performed at follow-up 1 month after stent removal in 30 of the 36 children (14 pyeloplasties, 16 ureteric reimplantations) showed the development of significant bacteriuria in 12 (40%) (Table). In this group, 4 had been treated by pyeloplasty (28% of the pyeloplasties performed) and 8 by ureteric reimplantation (50% of the reimplantations). Of the 3 patients with a previously infected stent, only 2 were observed at follow-up after 1 month and both showed significant bacteriuria in the mid-stream urine. The voiding cystourethrogram performed on 3 patients with the stent *in situ* showed grade I vesicoureteric reflux in the stented ureter in 2 cases.

Discussion

The occurrence of urinary tract infection induced by a stent is generally correlated to any or all of 3 different mechanisms: (1) introduction of bacteria during insertion of the stent, (2) entry of bacteria through the site of exit of the stent (urethral meatus, abdominal wall) and passage along the space between the stent itself and the ureteric mucosa, (3) ability of bacteria to rise through a column of fluid. All of these possibilities have been demonstrated experimentally in the presence of urethral catheters (Weyrauch and Bassit, 1951; Kass and Schneidermann, 1957) but are in principle also applicable to ureteric catheters. In the case of stents positioned during surgical operations, as in the present study, the 2 latter modes of contamination appear more likely, the stent having been inserted under sterile conditions in the operating theatre.

The results of the present study have demonstrated a low incidence (7.5%) of positive cultures in the urine from ureteric stents. In this regard, the importance of the role played by antibiotic cover, which was maintained until 15 days after the removal of the stent, is clearly evident. Kass and Schneidermann (1957) and Stark and Maki (1984), who studied the incidence of significant bacteriuria after 48 to 96 h with a urethral catheter *in situ* without antibiotic cover, reported markedly higher values of 40 to 100% positive cultures.

The possibility of contamination through the distal end of the stent emphasises the importance of effecting stent manipulation under sterile conditions.

An evaluation of the relationship between the type of surgery performed and the risk of contamination of the stent revealed that the percentage of post-operative bacteriuria with the stent *in situ* was higher in pyeloplasties (11.5%) than in ureteric reimplantations (5%), presumably due to the fact that the stents were maintained for a longer period in the pyeloplasties. Furthermore, in all of these patients the stent was brought out transurethrally.

The importance of vesicoureteric reflux, demonstrated in 2 of 3 patients in whom cystograms were carried out with the stent *in situ*, has not yet been established. In theory, this condition would favour the entry of bacteria into the ureter from the bladder and thus lead more easily to contamination of the upper tract. However, in these 2 patients with reflux, culture of urine from the stent was consistently sterile. Nevertheless, it should be pointed out that vesicoureteric reflux is of importance only in patients without permanent bladder drainage.

The incidence of positive cultures at follow-up 1 month after removal of the stent was higher (40%) than that observed in samples collected with the stent *in situ* (7.5%).

Despite the fact that 2 of the 3 children with infected urine resulting from the stent still presented a positive culture in the 30-day specimen, it should be remembered that (1) infected urine in the bladder does not mean infected urine in the upper tract previously drained by the ureteric stent, (2) in some of these children a suprapubic or urethral catheter had been used in the post-operative period, and (3) antibiotic cover was withdrawn 15 days after stent removal.

In conclusion, the use of ureteric stents in children submitted to reconstructive surgery leads, in our opinion, to a relatively low risk of urinary infection. Since this risk appears to increase the longer the stent remains *in situ*, early removal is advisable. Finally, the high incidence of significant bacteriuria observed at follow-up, 30 days after stent removal, indicates that long-term, low-dose antibiotic treatment is advisable in these young patients.

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Inverted Papilloma of the Ureter with Malignant Change

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Summary—Three patients with inverted papilloma of the ureter are described. A range of histological features was seen, including one showing malignant change. This condition, which is probably more common than previously thought, can be successfully treated by conservative surgery and close follow-up.

Inverted papilloma of the ureter has been described by Geisler *et al.* (1980) and, as with inverted papilloma of the bladder, there is debate as to whether the condition is always benign (Uyama and Moriwowi, 1981; Lausten *et al.*, 1984). We report a further 3 patients with inverted papilloma of the ureter. A review of ureteric tumours removed in this hospital since 1980 showed a 12% incidence (6/49) of tumours with an inverted papilloma pattern.

Case Reports

Patient 1. A 45-year-old male presented with a 7-year history of intermittent right loin pain which for the last 2 years had been associated with brown discolouration of the urine. He had no other urinary symptoms and his previous medical history was unremarkable. Physical examination was normal.

Intravenous urography showed a filling defect in the middle third of the right ureter with distension of the upper ureter. Retrograde ureterography demonstrated a freely mobile pedunculated polyp (Fig. 1). No abnormal cells were visible on cytological examination of the urine. The polyp was removed via a vertical ureterotomy, cutting the stalk at the base. The patient made an uneventful recovery.

Histological examination showed an inverted papilloma 2 cm in diameter, with a dome-shaped covering of attenuated regular transitional epithelium over infolded, and sometimes cystic, urothelium with a normal basal layer and regular maturation. There was neither stromal invasion nor inflammation.

Patient 2. A 64-year-old male presented with a 3-week history of intermittent right loin pain and haematuria. He had no significant previous history and physical examination was normal. Blood tests were normal, urine culture was sterile and cytological examination of the urine showed no abnormal cells.

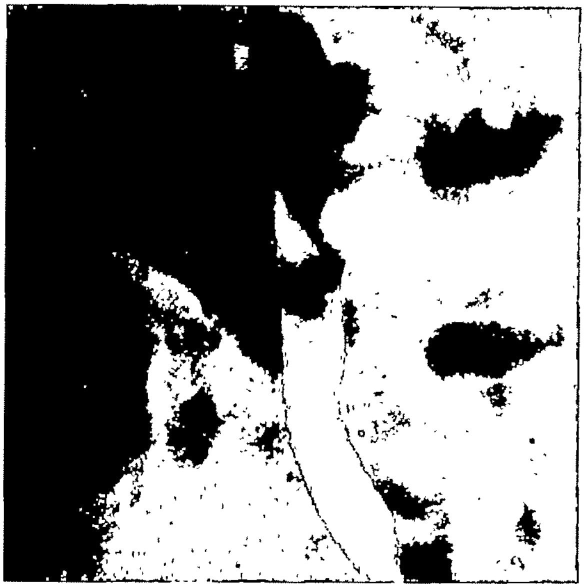

Fig. 1 Retrograde ureterogram in Patient 1 showing polypoid tumour on a thin stalk.

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IVU revealed a poorly functioning right kidney and ultrasound examination revealed dilatation of the upper tract. Percutaneous nephrostomy and antegrade ureterography demonstrated a polypoid filling defect in the lower ureter (Fig. 2). Since no dye had entered the bladder a retrograde ureterogram was performed which demonstrated a normal ureter below the obstruction. Cystoscopy was normal.

Surgery was performed to excise a bulky ureteric tumour with the adjacent segment of ureter. Histological examination confirmed a polypoid tumour (2 cm in diameter) with areas of a classical inverted papilloma (Fig. 3A), whilst elsewhere the appearances were of a low grade papillary transitional cell carcinoma (G1) without invasion (Fig. 3B).

Patient 3. A 63-year-old male had undergone a right nephro-ureterectomy 20 years previously for a low grade transitional cell carcinoma. Annual cystoscopies had been normal for 10 years. He then presented with a 4-month history of headaches, tiredness and anorexia. The only abnormal clinical finding was a blood pressure of 190/105. His blood urea was 16.4 mmol/l and creatinine 285 µmol/l; MSU and cytology were negative. An IVU demonstrated an obstructed left ureter; a percutaneous nephrostomy and antegrade ureterogram revealed a polypoid mass obstructing the lower third of the ureter. At operation, the lower 6 cm of ureter containing the tumour was excised and the remaining ureter reimplanted into a Boari flap. The tumour was 2.5 cm in diameter and histological examination showed the typical pattern of an inverted papilloma, but containing an area of papillary transitional cell carcinoma (G2) with limited invasion of the lamina propia (pT1) (Fig. 4). The surrounding ureteric mucosa was normal.

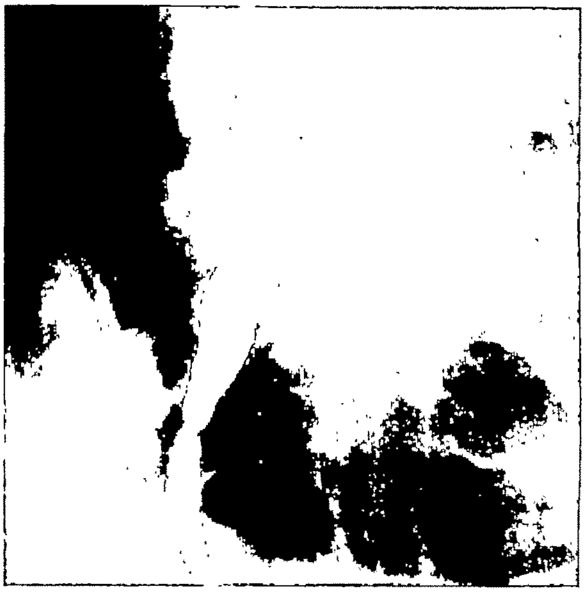

Fig. 2 Antegrade ureterogram in patient 2. A polypoid tumour is partially obstructing the right ureter.

Retrospective Review

We have since reviewed all ureteric tumours removed in Southmead Hospital since 1980. The

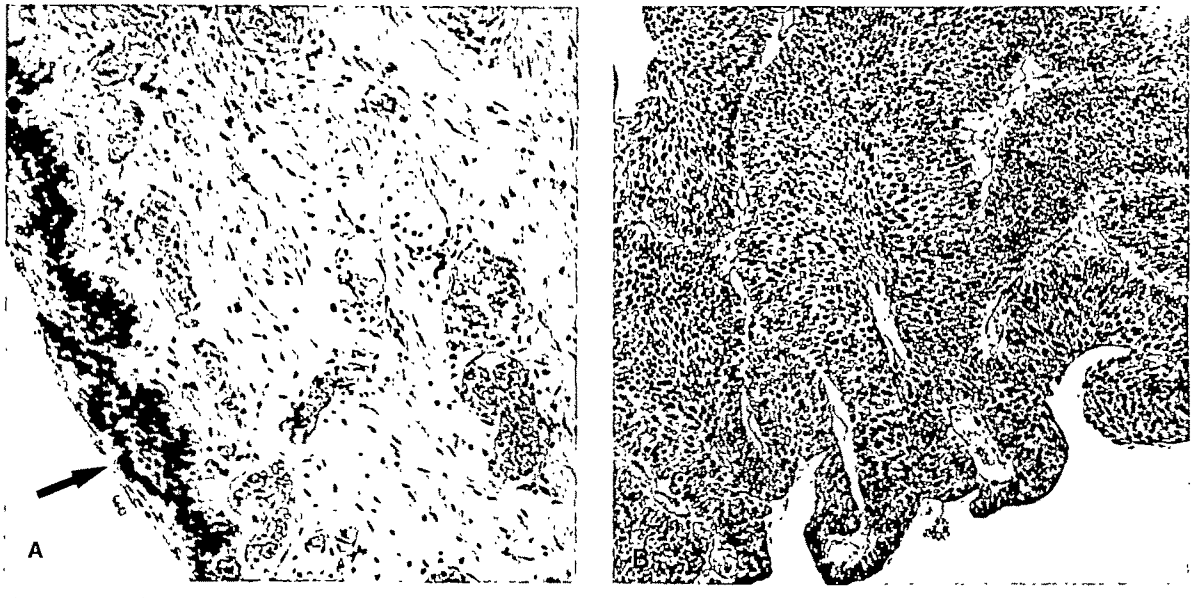

Fig. 3 Ureteric tumour from Patient 2. (A) Inverted papilloma pattern with a thin covering of normal urothelium (arrow). (H and E × 220). (B) Another are showing exophytic papillary transitional cell carcinoma. (H and E × 220).

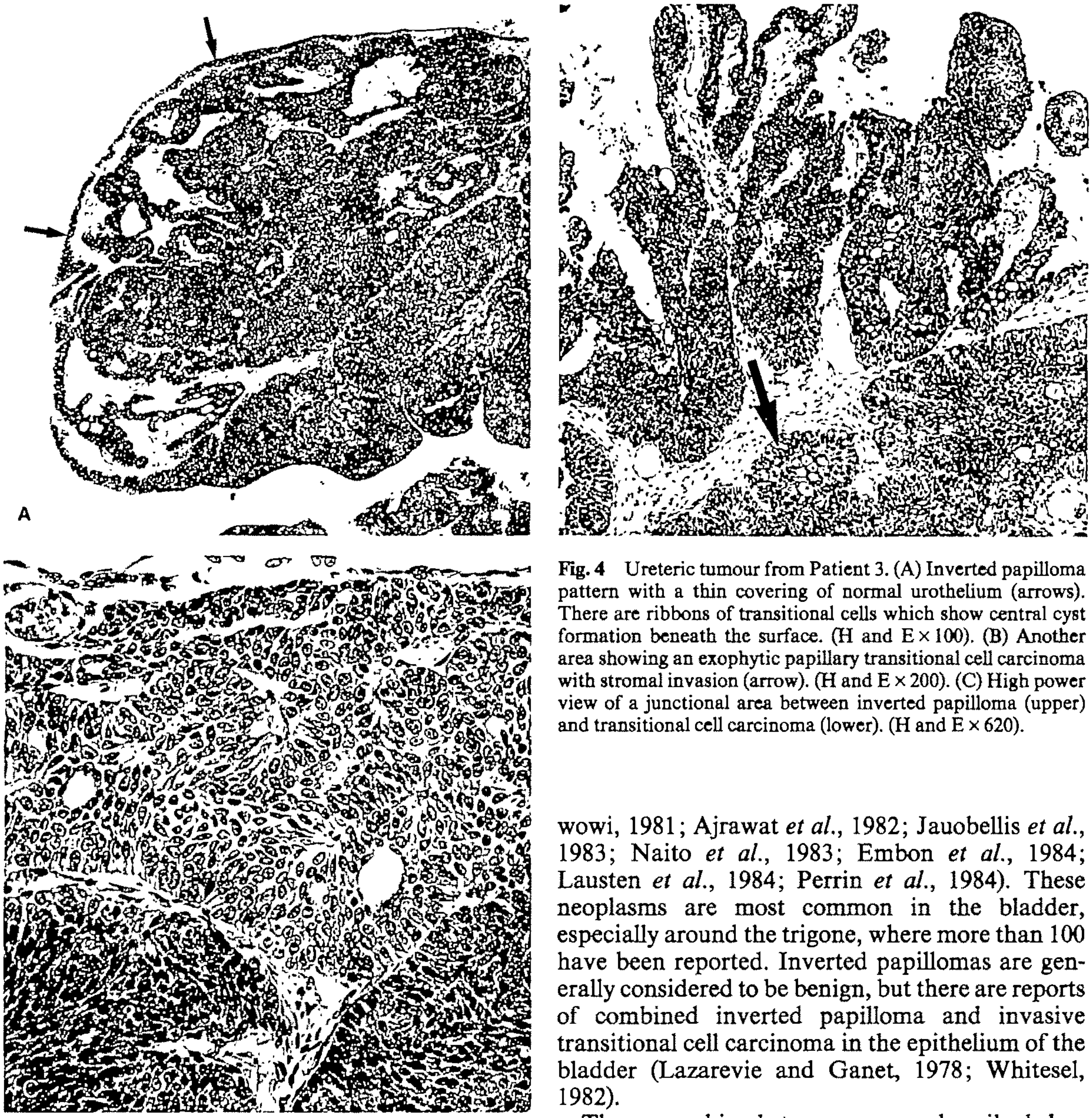

Fig. 4 Ureteric tumour from Patient 3. (A) Inverted papilloma pattern with a thin covering of normal urothelium (arrows). There are ribbons of transitional cells which show central cyst formation beneath the surface. (H and E × 100). (B) Another area showing an exophytic papillary transitional cell carcinoma with stromal invasion (arrow). (H and E × 200). (C) High power view of a junctional area between inverted papilloma (upper) and transitional cell carcinoma (lower). (H and E × 620).

total number was 49, of which 6 (12%) were considered to show features of an inverted papilloma; the remainder were papillary transitional cell carcinomas.

Discussion

Inverted papilloma is a rare tumour of the ureter and to date 15 have been described (DiCello *et al.*, 1980; Geisler *et al.*, 1980; Fromowitz *et al.*, 1981; Silverstein and Carter, 1981; Uyama and Moriwowi, 1981; Ajrawat *et al.*, 1982; Jauobellis *et al.*, 1983; Naito *et al.*, 1983; Embon *et al.*, 1984; Lausten *et al.*, 1984; Perrin *et al.*, 1984). These neoplasms are most common in the bladder, especially around the trigone, where more than 100 have been reported. Inverted papillomas are generally considered to be benign, but there are reports of combined inverted papilloma and invasive transitional cell carcinoma in the epithelium of the bladder (Lazarevie and Ganet, 1978; Whitesel, 1982).

These combined tumours are described less frequently in the upper urinary tract, but Uyama and Moriwowi (1981) reported carcinomatous areas in an inverted papilloma of the renal pelvis. Lausten *et al.* (1984) reported a case of an inverted papilloma with malignant change of the lower ureter. They also found that 2 of their 4 patients with upper urinary tract inverted papilloma had a history of transitional cell carcinoma elsewhere in the urinary tract, whilst another developed a transitional cell carcinoma of the renal pelvis 8 years after an upper tract inverted papilloma had been removed. This is very similar to our Patient 3, who had also undergone a previous resection for transitional cell carcinoma.

Schulze *et al.* (1986) reported a satellite inverted papilloma close to the main tumour in the renal pelvis. In a further case an inverted papilloma was successfully removed, only to be followed several months later by the development of a bladder adenocarcinoma (Fromowitz *et al.*, 1981) and another patient had previously had a renal carcinoma (Silverstein and Carter, 1981).

There are 2 other reports of synchronous transitional cell carcinoma and inverted papilloma of the upper urinary tract (Anderstrom *et al.*, 1982; Jauobellis *et al.*, 1983). It is now believed that inverted papilloma represents a true neoplastic growth which can be easily differentiated histologically from transitional cell carcinoma. The 2 cases described here, and the 2 previously reported cases of malignant change in an upper tract inverted papilloma (Uyama and Moriwowi, 1981; Lausten *et al.*, 1984), suggest that inverted papilloma may show a series of changes from benign papilloma to transitional cell carcinoma. The pure inverted papilloma behaves like a benign tumour, but other tumours show a mixed pattern, part carcinoma and part inverted papilloma. Recognition of this mixed pattern is essential when assessing behaviour and the degree of tumour invasion. The most useful diagnostic feature of inverted papilloma in a mixed tumour is an attenuated but continuous layer of urothelium on the surface of the inverted papilloma with underlying regularity of the deeper epithelial cells. Both inverted papillomas and transitional cell carcinomas are likely to have the same aetiology, as suggested by the number of patients in whom there was a synchronous or a metachronous urothelial tumour.

Although no recurrence of pure inverted papilloma has been reported, careful follow-up of patients with an upper tract inverted papilloma is essential as they may subsequently develop other transitional cell carcinomas. Inverted papillomas with areas of transitional cell carcinoma can be expected to develop according to the worst component of the tumour. Nevertheless, these tumours can be safely managed by local resection provided careful follow-up is arranged.

Eighteen inverted papillomas of the ureter have been described to date, of which 3 have shown malignant change, and 5 patients have had a separate urothelial tumour. It is likely that these tumours have previously been under-recognised, as this review of pathology records found that 12% of ureteric tumours contained an inverted papilloma pattern. These tumours must be considered in the differential diagnosis of ureteric lesions in order to avoid needless major surgery. It is important to recognise that the inverted papilloma may not be a distinct tumour but that it should be classified as a variant of the usual transitional cell tumour.

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Acceleration of Flow Rate as a Screening Test for Detrusor Instability in Women with Stress Incontinence

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Summary—Forty females with urinary stress incontinence (mean age 52 ± 10 years) and 20 age-matched controls (mean age 49 ± 15 years) underwent complete urodynamic evaluation. In the former group, all patients complained of irritative bladder symptoms (frequency, nocturia, urgency) and 20 of them (Group B) showed detrusor instability (DI); in the other 20 (Group A) a final urodynamic diagnosis of genuine stress incontinence (GSI) was made. Instability was not apparent in Group B at standard filling cystometry, but had to be elicited through aggressively stressing the bladder by provocation tests.

In all women the acceleration of flow rate ($\bar{a}$, in ml/s^2) was calculated from free flow uroflowmetry as the ratio of peak flow divided by the time to peak flow. This parameter did not differ significantly in GSI patients when compared with controls but proved higher in the DI group than in either the controls or the GSI patients.

It was concluded that measuring the acceleration of flow rate is a simple and reliable test which improves the accuracy of diagnosis of detrusor instability in stress incontinent women.

The acceleration of flow rate is a simple urodynamic parameter which has been described by Susset (1983). It can be easily derived from free flow uroflowmetry and is independent of the urinary volume voided.

This parameter is proposed as a reliable test to improve the accuracy of diagnosis of detrusor instability in stress incontinent women.

Patients and Methods

All female patients referred to our urodynamic unit during the last 2 years with urinary stress incontinence were divided into 2 groups: those with a final urodynamic diagnosis of genuine stress incontinence and those in whom detrusor instability was ascertained. For each of the 2 groups, 20 patients were studied.

Urodynamic evaluation comprised free flow uroflowmetry (performed with the patient voiding in private and recorded by means of a standard weight flowmeter), urethral pressure profilometry and medium fill water cystometry with both external urethral sphincter electromyography and pressure flow studies. During cystometry, which was performed with the patient in the sitting position, care was taken to note the occurrence of unstable detrusor contractions. When no such contractions were evident, the bladder was stressed by a series of provocation tests including rapid filling, coughing, straining and jumping on the spot.

The 20 patients in each group all complained of irritative bladder symptoms (frequency, nocturia, urgency): in Group A (GSI) the mean age was 53 ± 10 years and in Group B (DI) it was 51 ± 11 years. In Group B, DI was not apparent at standard filling cystometry, but only when bladder stress was induced by provocation tests.

The control group C comprised 20 age-matched females (mean age 49 ± 15 years) referred with recurrent urinary infections (but with no sign of infection at the time of urodynamic evaluation and no pathological findings at cystoscopy and/or cystography). No member of this group had irritative bladder symptoms when examined at our unit or during the intervals between recurrences of

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urinary infection. Group C females also underwent a complete urodynamic investigation as previously described, with no abnormalities of any type being discovered.

Women suffering from urethral stenosis; bladder cancer or stones; metabolic, neurological or mental diseases; those with a positive urine culture or undergoing treatment with drugs that could interfere with bladder filling or voiding, were excluded from the study.

In each patient the acceleration of flow rate ($\bar{a}$, in ml/s^2) was derived from free flow uroflowmetry as the ratio of peak flow (in ml/s) divided by the time to peak flow (in s).

Averages and standard deviations of $\bar{a}$ were calculated for each group. Data were evaluated by both non-parametric and parametric statistical methods (Kruskal-Wallis's and Scheffé's tests and Dunn's multiple-comparison procedure). These tests were also used to check the significance of any differences between patients' ages in the 3 groups.

Methods, definitions and units conformed to the standards proposed by the International Continence Society (Abrams *et al.*, 1988) except where specifically noted.

Results

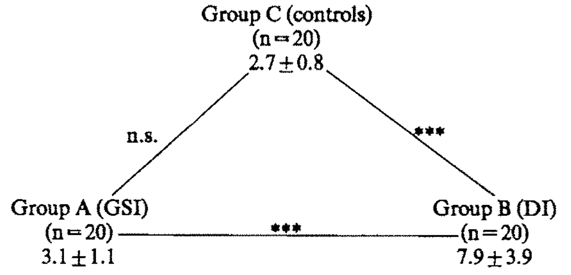
The patients' ages ranged from 24 to 75 years (mean ± SD 49 ± 15) in controls, from 32 to 69 years (53 ± 10) in Group A and from 23 to 65 years (51 ± 11) in Group B. Mean values did not differ significantly in the three groups.

No abnormalities were found during electromyography or pressure flow studies in any patient. Filling cystometry showed no relevant findings other than the presence, in Group B, of uninhibited detrusor contractions when stressing the bladder by provocation tests. Urethral pressure profilometry yielded normal results in the control group, whilst Groups A and B showed, on average, lower than normal values of both maximum urethral closure pressure and functional urethral length.

Individual values of $\bar{a}$ (in ml/s^2) ranged from 1.3 to 3.8 in Group C, from 1.6 to 4.8 in Group A, and from 5.1 to 21.0 in Group B. Mean values did not differ significantly in the GSI patients and the control group, but highly significant differences were found between the DI group and both the GSI and the control patients.

Averages and standard deviations of the parameter $\bar{a}$ for the 3 groups, and significance levels of difference are shown in the Table.

Table Statistical Data



Kruskal-Wallis's test: $\chi^2 = 39.805$ ($P < 0.0005$).
Scheffé's test: $F = 28.50$ ($P < 0.001$).
*** = $P < 0.001$ (Scheffé's test and Dunn's multiple-comparison procedure).

Discussion

It is common experience that the vast majority of women with urinary stress incontinence suffer from irritative bladder symptoms (frequency, nocturia, urgency), whilst a minority report stress incontinence as the only complaint (Kaufman, 1979). This poses the problem of ruling out detrusor instability and is of great importance in the planning of treatment.

Normally, poor correlation is found between irritative bladder symptoms and the presence of unstable detrusor contractions. Thus filling cystometry is mandatory (Torrens, 1984), but it is well known that in nearly 50% of women with unstable bladders, uninhibited detrusor contractions are elicited only by aggressive provocation tests (Turner-Warwick and Brown, 1979).

In the present study, all females investigated for urinary stress incontinence reported irritative bladder symptoms. Urodynamic evaluation showed detrusor instability in 20, whilst the other 20 had genuine stress incontinence.

For the DI group, patients were chosen in whom standard filling cystometry failed to reveal uninhibited detrusor contractions, which could only be elicited by provocation tests.

It should be noted that, at free flow uroflowmetry, the DI patients showed a significantly higher acceleration of flow rate than that found in the women with GSI as well as in the controls (Table). In other words, low values of $\bar{a}$ (<5 ml/s^2) do not seem to correlate with the presence of uninhibited bladder contractions, whilst high values (>5 ml/s^2) would be closely associated with detrusor instability.

In stress incontinent women with irritative bladder symptoms, therefore, a low acceleration of flow rate is proposed as a reliable test to eliminate false negative diagnoses of DI (*i.e.*, to confirm the absence of uninhibited detrusor contractions at standard filling cystometry). This would obviate the need for aggressive provocation.

On the other hand, high values of $\bar{a}$ indicate the need for provocation tests when standard cystometry does not show unstable contractions. Should aggressive provocation fail, then high values of $\bar{a}$ alone might justify a satisfactory (though indirect) diagnosis of DI.

Further investigations are needed to confirm these arguments. On the basis of these preliminary results, however, it is suggested that free flow uroflowmetry, with assessment of the parameter $\bar{a}$, should always precede more invasive urodynamics in stress incontinent women. This would lead to a more accurate diagnosis of DI in such patients.

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Clean Intermittent Self-catheterisation in 172 Adults

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Summary—We report the results of clean intermittent self-catheterisation (CISC) in 172 adults (68 male, 104 female). Seven patients were unable or unwilling to master the technique and 145 still remain on CISC, representing a total experience of 6981 patient-months. Ten patients required readmission: 5 for retraining and 5 for complications (average hospital stay 2.4 days); 123/163 patients catheterised themselves every 3 to 4 h and 92 were continent on CISC; of the 107 patients incontinent prior to starting CISC, 101 were improved; 70 patients had no infections whilst on CISC, the mean infection rate being 1 per 14 patient-months; 29% of patients experienced persistent urethral bleeding; 156/163 patients were satisfied or very satisfied with CISC and 140 found the technique easy or very easy; 76 patients had never visited their GP for a urinary problem whilst using CISC and the mean rate was 1 visit per 8 patient-months. CISC is an easily learnt technique that is safe and acceptable to patients, and one which places few extra burdens on hospital or community resources.

A wide variety of urological conditions can result in a bladder which does not empty well and large volumes of residual urine may predispose to infection, stone formation, detrusor dysfunction and upper trace dilatation with associated renal damage. Such were the frequency and severity of these complications in the past that many patients underwent operations such as cutaneous vesicostomy (Lapides *et al.*, 1960) or the insertion of indwelling urethral or suprapubic catheters (Guttman and Franckel, 1966), but these are not without problems. The use of sterile intermittent catheterisation in the management of traumatic spinal injury was introduced by Guttmann in 1947 (Guttmann and Frankel, 1966), though this was slow to gain acceptance. When Comarr (1972) introduced the technique to the Rancho hospital a lack of trained paramedical staff led to the development of sterile intermittent self-catheterisation in paraplegics, leaving the technicians free to catheterise the tetraplegics. No significant differences in infection rate or other complications were reported between these 2 groups of patients. Lapides *et al.* (1972) went on to develop the use of intermittent self-catheterisation in 14 patients with high residual urine volumes caused by neurovesical dysfunction, who had experienced repeated urinary infections due, it was thought, to bladder wall ischaemia resulting from increased tension. Lapides *et al.* (1972) further reasoned that complete bladder emptying would allow the natural defensive mechanisms within the bladder wall to deal with any bacteria introduced by the catheter and thus introduced clean intermittent self-catheterisation. Since 1979, 172 patients have been treated by CISC at the Freeman Hospital and we have reviewed the results up to December 1988.

Patients and Methods

All patients using intermittent self-catheterisation were taught the technique by A.L.L. They were contacted by letter or seen in the out-patient clinic and asked to complete a 3-page questionnaire (Table). Non responders were sent further questionnaires and contacted by telephone; 2 patients did not reply because of illiteracy but completed a telephone questionnaire. In addition, each patient's family doctor was contacted and the hospital notes were reviewed.

Based on a Poster Demonstration at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

Table Layout of Questionnaire

General	Reason(s) for starting CISC Length of time on CISC Reasons(s) for discontinuing
Technique	Type of catheter/previous catheter(s) Problems with passage of catheter and any remedy Ease of technique (scale from impossible to easy)
Outcome	Continence before and during CISC Additional continence aids used Patient's perception of outcome Infections before and during CISC (Bladder/kidney/other)
Complications	Pain/bleeding/stricture/stone/other
Consultations	Family doctor/incontinence advisor/other
Patient satisfaction and comments	

Between October 1978 and July 1988, 172 patients were treated by CISC (68 male, 104 female). The mean age at the start of CISC was 53 years (range 17–83). The age distribution was bimodal with a peak in the third decade due to congenital neuropathies, spinal injuries and multiple sclerosis and a second peak in the sixth decade due to pelvic surgery, lumbar disc prolapse and chronic retention of unknown aetiology. The underlying conditions are shown in Figure 1.

Patients were introduced to CISC if, following urological assessment, they were judged to have an adequate bladder capacity and a competent sphincter mechanism and if, after clinical assessment, the continence advisor, medical and nursing staff considered that the patient's mental capacity, motivation and manual dexterity would allow CISC to be performed satisfactorily.

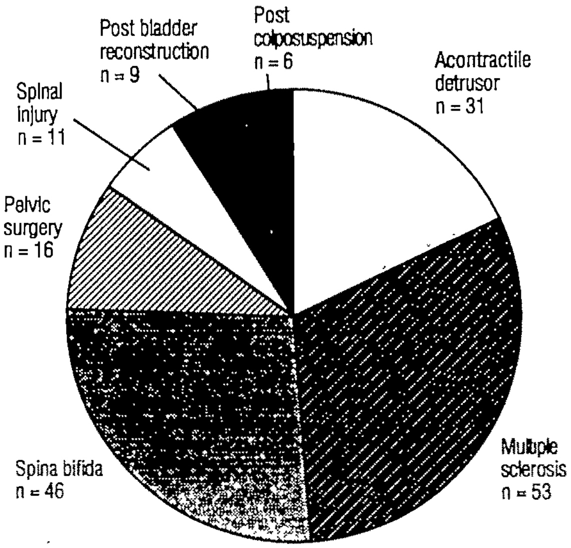

Fig. 1 Clinical diagnoses of all patients on CISC.

Results

All 172 patients were admitted for assessment and initial instruction in CISC, the mean length of stay for this purpose being 2 days (range 1–3); 10 patients were readmitted whilst on CISC; 5 required reassessment of technique (as day cases) and a further 5 required admission for complications (mean stay 3.8 days). One patient required removal under anaesthesia of a knotted catheter, 2 developed urethral strictures and presented in acute retention unable to pass a catheter and 2 were admitted with urinary infections.

Of 172 patients, 27 (15%) are no longer using CISC; 4 patients (3 female, 1 male; mean age 67 years) were unwilling to learn the technique and gave up 1 day (3 patients) and 1 week (1 patient) after the start of treatment; 3 were able to perform the technique but preferred to use indwelling catheters. Thus 165 patients were discharged using CISC; 2 died following progression of their underlying disease, leaving 163 patients in the study group. In 15 cases CISC was no longer needed when the initiating factor resolved. Residual urine volumes decreased in 5 patients after colposuspension, in 7 patients with acontractile detrusors of unknown origin and in 3 patients with neuropathic bladders following pelvic surgery. In 3 patients CISC was stopped because of progression of disease and general disability and an indwelling catheter was used. In 3 other patients catheterisation was performed by the spouse because the patient had poor hand control and progressive disability.

The frequency of catheterisation is presented in Figure 2.

Prior to treatment with CISC, 107 patients (65%) were incontinent. Continence was achieved by CISC alone in 37 (35%); 28 (26%) were incontinent once a month or less; 14 (13%) were incontinent once a week or less and 28 were incontinent every day, although in 8 of these incontinence occurred only at night; 94% of patients reported an improvement in their continence since starting CISC.

Symptomatic infection rates were available in 153 patients; 70 (48%) had never had a symptomatic infection (a total of 1187 infection-free patient-months) and 22 (14%) reported only 1 infection (mean time on treatment 32 months); 32 patients (21%) reported infection rates of less than 1 per year, 9 (6%) recorded 2 infections per year, 12 (8%)

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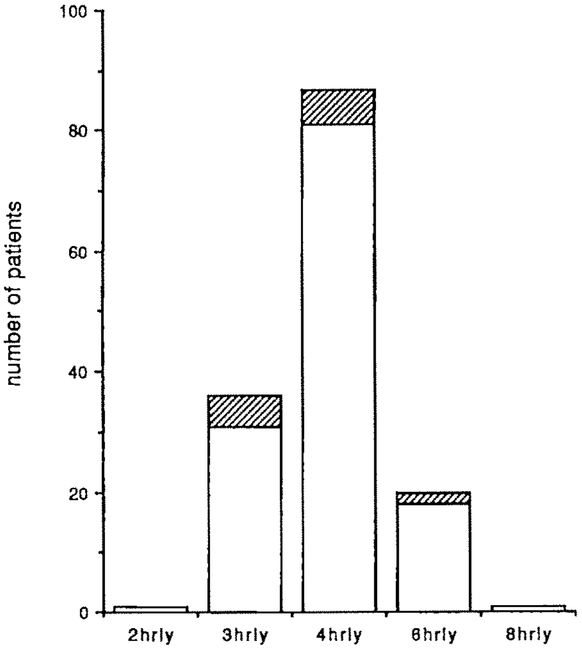

Fig. 2 Frequency of catheterisation. Shaded areas represent patients whose sleep was disturbed by the need to self-catheterise.

had 4 infections per year and 8 (5%) complained of 6 or more infections per year. The mean infection rate was 1 per 8 patient-months. In 78 patients a catheter specimen of urine was taken when the patient was asymptomatic and in 41 cases (52.5%) this was sterile.

Other complications were observed less frequently. Of 163 patients on whom data were available, 121 (74%) complained of initial bleeding on starting CISC and 45 (29 male, 16 female) (28%) complained of persistent urethral bleeding 3 months after starting CISC; 2 patients reported blood throughout the urinary stream and were investigated by IVU and cystoscopy: no abnormality was found; 2 patients (1 male, 1 female) developed urethral strictures 30 months and 43 months after the start of CISC. The male patient required an optical urethrotomy and both patients now use "Lofric" catheters without difficulty. Four men developed recurrent epididymo-orchitis and 2 underwent vasectomy with good results; 1 male patient required removal of his catheter under anaesthesia when it became knotted in his bladder; 16 patients (10 male, 6 female) complained of pain during catheterisation and in 9 of these the pain was mainly on withdrawal of the catheter.

Family doctors were also contacted by questionnaire and 138 doctors looking after 165 patients on CISC replied; 73 patients had never visited their GP specifically about a urological problem; 41 recorded 1 visit per year, 35 recorded 2 visits per year, 6 recorded 4 visits per year, 4 recorded 6 visits per year and 6 recorded 12 visits per year. The mean rate of consultation was 1 per 14 patient-months. Consultations were usually for treatment of urinary infection or for obtaining supplies of catheters; 5 consultations were for pain, 2 for epididymitis and 1 for acute retention.

Patients were asked to comment on their satisfaction with CISC and 159 replied; 126 were very satisfied, 30 were satisfied and only 3 were not satisfied. The reasons given for dissatisfaction were persistent incontinence (1), recurrent infection (1) and finding the technique distasteful (1); 153 patients found the technique easy, 3 found it difficult and 3 patients who found it impossible because of their disability were catheterised by their spouses.

Discussion

Intermittent self-catheterisation is an essential technique for the urologist to be able to offer to patients with impaired bladder emptying. The technique is quickly learnt and acceptable to most patients of both sexes and a wide age range. Few reports have dealt with patient selection. Whitelaw *et al.* (1987) reported an early drop-out rate of 20% in an elderly population and cited good mental attitude and motivation as being more important than visual acuity and manual dexterity in predicting a successful outcome. Diokno *et al.* (1983) regarded adequate bladder capacity, adequate sphincter function and manual dexterity as vital factors in ensuring a successful outcome and reported a 10-year follow-up study of 60 patients on CISC in which 17 discontinued treatment; the largest group (10) stopped because bladder function recovered; deteriorating neurological function prevented 4 from continuing and the other 3 stopped because of persistent incontinence, dissatisfaction with the technique by the patient's parent and a urethral false passage. The latter problem is perhaps the only absolute contra-indication to CISC. Similar results were reported by Murray *et al.* (1984). We believe that careful clinical and urodynamic selection of patients has resulted in our low initial failure rate. However, it could be argued that by widening our selection criteria a few more patients might have benefited from a trial of CISC. The patients have also had easy access to advice from a continence advisor and this, we believe, has contributed to the low late failure rate.

Our continence rates appear somewhat worse than those previously reported; for example, Lapides *et al.* (1974) reported that 97% were dry on CISC alone. However, all of these patients had suprasacral spinal lesions and may have been continent prior to treatment. In other series reporting CISC in a population with mixed disorders, the continence rate was approximately 40% diurnal incontinence and 35% nocturnal incontinence alone (Murray *et al.*, 1984).

Our symptomatic infection rates were similar to those reported previously, even though the patient groups were widely different. Thus Lapides *et al.* (1976) reported that 41% of patients were free of all infection and Maynard and Glass (1987) claimed that 32% had suffered no more than 1 infection whilst on CISC. The results of bacteriological examination of catheter specimens of urine taken from asymptomatic patients ranged from 14% sterile to 43% contaminated (Murray *et al.*, 1984) to 47% sterile (Whitelaw *et al.*, 1987) and 66% sterile (Lapides *et al.*, 1974). These compare favourably with sterile urine in 62% of males and 49% of females on sterile intermittent catheterisation (Guttman and Frankel, 1966).

The incidence of other complications was similar to that reported by others: epididymitis varied between 2% (Lapides *et al.*, 1976) and 9% (Maynard and Glass, 1987); urethral strictures were found in 2/19 patients (Whitelaw *et al.*, 1987) and 2/34 patients (Maynard and Glass, 1987); a false passage occurred in 1/34 (Maynard and Glass, 1987) and discomfort in 14% (Murray *et al.*, 1984). In Newcastle, patients using CISC have made few demands upon the hospital or community services, a finding noted in paraplegics by Maynard and Glass, 1987.

In the present series, upper tract dilatation present at the start of CISC has either remained static or resolved, although deterioration of renal function during treatment with CISC has been reported and regular follow-up is required (Perkash, 1978).

We consider CISC to be a widely applicable, safe and effective treatment which is acceptable to patients and has added little to the workload of our department or the community services.

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Neodymium-YAG Laser Irradiation of Stage T2 Muscle-invasive Bladder Cancer. Long-term Results

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Summary—The study group consisted of 15 patients with solitary stage T2 bladder tumours treated with transurethral resection (TUR) and subsequent neodymium-YAG laser irradiation.

Ten patients are alive without evidence of cancer 56 to 78 months (mean 67) after treatment; 1 died of cardiovascular disease 2 years after treatment and autopsy revealed no cancer. In 4 patients the treatment failed and cystectomy or external beam radiation was carried out.

The long-term results indicate the combination of TUR and laser irradiation to be beneficial in the management of T2 tumours in selected cases.

Neodymium-YAG laser irradiation, alone or subsequent to transurethral electro-resection, is a widely accepted and established treatment of superficial bladder tumours. Local recurrence rates of approximately 5% have been reported (Hofstetter, 1981; Rothenberger *et al.*, 1983; Smith and Middleton, 1985; Beisland and Seland, 1986), but the laser does not seem to decrease the incidence of new tumours in remote areas (Beisland *et al.*, 1985; Beisland and Seland, 1986; Arkell and Randall, 1988) if not combined with intravesical chemotherapy (Hofstetter *et al.*, 1985).

The YAG laser light produces a homogeneous coagulation 5 to 6 mm into bladder tissue. It is therefore possible to perform transmural coagulation of the bladder, making the laser suitable for treatment of muscle-invasive tumours (Beisland, 1986).

Previous reports on laser irradiation of muscle-invasive tumours mainly describe the procedures and short-term results (Hofstetter *et al.*, 1982; McPhee *et al.*, 1982; Smith, 1986) and indications for laser treatment were limited to patients who were not candidates for (or who refused) radical surgery.

We report on the long-term results in patients who were candidates for radical therapy and were offered laser irradiation as definitive management of their disease.

Patients and Methods

The series comprised 10 men and 5 women aged between 60 and 85 years (mean 70). All had solitary primary stage T2 tumours without carcinoma *in situ* or severe epithelial dysplasia in mapping biopsies; 9 tumours were moderately differentiated (WHO grade II) and 6 were WHO grade III. Clinical staging was performed by urethrocystoscopy, bimanual palpation of the bladder and pathological examination of the TUR specimen. Distant metastases were screened by X-ray, ultrasound scanning of the liver and retroperitoneum, serum chemistry studies and intravenous urography.

All macroscopic tumour was removed by conventional electro-resection into macroscopically normal bladder tissue. No residual tumour was present on bimanual palpation after resection.

One or 2 weeks later the tumour bed and surrounding mucosa were coagulated by the neodymium-YAG laser under local anaesthesia of the urethra. Using a laser power of 45 to 50 W, the area to be coagulated was systematically irradiated by overlapping single pulses of 4 seconds' duration. There was no need for a bladder catheter post-

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operatively and the patients left hospital the same afternoon or next morning.

Follow-up examinations were carried out every 3 months for the first 2 years and then at 6-monthly intervals. Investigations included urethrocystoscopy, bimanual palpation of the bladder, urine cytology and forceps biopsies from the treated area, its margin and from selected sites. After 2 years' disease-free follow-up, biopsies were taken only if suspicious areas were present in the bladder.

The patients were treated between June 1982 and June 1984. The final evaluation was carried out in December 1988 and the observation period ranged from 54 to 78 months.

Results

The results are shown in the Table.

Ten patients are alive without evidence of cancer 56 to 78 months (mean 67) after treatment. Their original tumour grading was WHO II in 7 cases and WHO III in 3. In 3 cases (all WHO II), new small superficial tumours occurred in remote areas. There was no progression in histological differentiation and the tumours were easily treated by laser coagulation.

One patient died of cardiovascular disease 2 years after treatment. No tumour could be found at autopsy.

Local tumour recurrence occured 3 to 12 months after treatment in 4 patients. Their original tumour grading was WHO III in 3 cases and WHO II in 1. All had radical cystectomy or external beam radiation; 1 patient died from disseminated cancer 1 year after cystectomy. The others are still alive.

There were no complications due to laser irradiation.

Discussion

All patients in this series had clinical T2 tumours confirmed at histology. In accordance with the TNM classification system, all had tumour-free muscle tissue at the base of the resection site and no tumour was palpable bimanually following resection. Only patients with primary and solitary tumours were treated.

An interval of 1 to 2 weeks between TUR and laser irradiation ensures a regular tumour bed with no blood clots. This is necessary for optimal penetration of the laser light into tissue. The time interval between the 2 procedures depends on the extent of the resection.

Using the recommended laser power, the vaporising or ablative effect of the YAG laser is minimal and no perforations of the bladder have occurred. The transmural coagulation necrosis is gradually replaced by collagen fibres. The elastic framework of the wall remains intact during the period of restitution and the risk of secondary bladder perforation is minimal.

The total amount of laser energy applied is irrelevant, but transmural coagulation is essential. Single pulses of 45 to 50 W for 4 s seem optimal (Beisland, 1986).

Intestinal tissue is more sensitive to heat than bladder tissue (Kronester *et al.*, 1981). To avoid damage to adjacent intestines, the laser power or the irradiation time should be reduced when the bladder wall is thin due to deep electro-resection, particularly when the area to be irradiated is located in the dome. Bowel damage did not occur in the present series, but we have experienced 3 small bowel perforations in approximately 1000 laser treatments of bladder tumours in this department.

The distinction in the TNM system between T2 and T3 tumours enables tumours which can be treated by local procedures to be distinguished from those which require radical therapy. Conservative treatment of T2 tumours, however, gives poor results. Despite a careful selection of T2 tumours suitable for TUR, Barnes *et al.* (1977) reported a 5-year survival rate of only 31%. Better results are obtained with radical cystectomy, which is the

Table Results of Neodymium-YAG Laser Irradiation of T2 Muscle-invasive Bladder Cancer

		Histological differentiation of primary tumour		
	No. of patients	*WHO II*	*WHO III*	*Observation time or time to recurrence (months)*
Alive without cancer	10	7	3	56–78
Dead without cancer	1	1		24
Failures	4	1	3	3–12

method most commonly recommended. A survey of published results reported a 5-year survival rate of 44 to 86% for T2 tumours (Jacobi *et al.*, 1983). Our series is too small and too selective for comparison with results obtained by other methods. A 5-year survival rate of 67% with no evidence of tumour recurrence is encouraging, however, and justifies continued development of the method.

In a previous prospective study we compared TUR of bladder tumours with TUR plus laser irradiation (Beisland and Seland, 1986); 6 of 10 T2 tumours (60%) treated by TUR alone recurred in the treated area within 2 years compared with 3 of 15 tumours (20%) which received additional laser irradiation. Most of the recurrences in the TUR group developed within 3 months of resection.

The reasons for the improved results obtained by additional laser irradiation are not clearly understood. The tissue defect after TUR may provide a fertile surface for implantation of tumour cells exfoliated during the procedure. Any implanted cells may be destroyed by the subsequent laser treatment. In addition, laser irradition may effectively destroy malignant cells remaining in the muscle tissue after an incomplete resection.

Despite the satisfactory results in our series, there remain many problems to be solved before the laser can be recommended as a reliable alternative to radical cystectomy. Improved methods for preoperative staging and thorough follow-up are necessary. Intravesical ultrasonography, computed tomography and nuclear magnetic resonance imaging are promising modalities in this regard. Peroperative imaging techniques to visualise the depth of coagulation is desirable. With the present endoscopic irradiation technique it is impossible to guarantee transmural coagulation in all parts of the tumour. Endoscopic laser treatment has been performed under pelvioscopy or laparoscopy control in order to visualise coagulation on the outer surface of the bladder (Kriegmair *et al.*, 1988). If done under laparotomy control, additional laser irradiation from the outside of the bladder becomes possible, and staging lymphadenectomy can be carried out. Lymph node involvement at the time of diagnosis is a poor prognostic sign (Smith and Whitemore, 1981) which calls for adjuvant therapy.

Haematogenous or lymphogenous spread of malignant cells during TUR or the presence of undetectable micrometastases at the time of diagnosis is a possibility. An investigation into the possible beneficial effect of systemic chemotherapy administered prior to local treatment or in the period between TUR and laser coagulation will be initiated in this department in the near future. The development of safe bladder-preserving procedures, in order to improve the patients' quality of life, should provide a challenge to urological surgeons.

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Estimation of Growth Fraction *in situ* in Human Bladder Cancer with Bromodeoxyuridine Labelling

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Summary—A group of 8 patients with invasive bladder cancer received fractionated intra-arterial infusions of the thymidine analogue bromodeoxyuridine (BrdU), 150 mg, every 6 to 10 h for 3 days before endoscopic cold cup biopsy to label tumour cells in the proliferative pool (growth fraction). The tumour specimens were fixed and stained by an indirect immunoperoxidase method using anti-BrdU monoclonal antibody. There was an area which could not be stained with anti-BrdU monoclonal antibody surrounding the stained area where diffusion effects could be excluded. This indicates a growth fraction < 1 and implies that a proportion of the tumour cells in bladder tumours are cycling and contributing to growth. The BrdU labelling index (growth fraction) was determined by counting the number of BrdU labelled cells in the well labelled tissue sections. The average growth fraction of invasive bladder cancer was 38.4 ± 7.7% (range 26.9–48.1%). Grade 3 tumours averaged 42.8 ± 5.4% labelling versus 31.0 ± 4.4% in grade 2. The higher growth fraction may indicate greater biological malignancy. These results indicate that immunohistochemical studies of cell kinetics using BrdU monoclonal antibodies may provide information about the biological characteristics of bladder tumours *in situ*.

Mendelsohn (1962) introduced methods of calculation into cell population kinetics and growth fraction was first defined mathematically as the number of proliferating cells divided by the total cell population. Fractionated exposure of a cell population to ^{3}H-thymidine for a period at least as long as the cell cycle time gives an approximation of the growth fraction. All cycling cells pass through the S phase during that period and will incorporate ^{3}H-thymidine. Cells that fail to incorporate thymidine are considered non-cycling (or Go) cells. As might be expected, fractionated injections of ^{3}H-thymidine proved extremely difficult to perform, being hazardous to both patient and environment.

The development of a monoclonal antibody able to identify nuclei containing bromodeoxyuridine was a breakthrough in the study of cell kinetics of tumours *in situ* (Gratzner, 1982; Hoshino *et al.*, 1985, 1986). BrdU is one of the halopyrimidines and, like thymidine, is incorporated into cellular nuclei at the time of DNA synthesis for mitosis. The S phase fraction can be defined by short-term exposure to BrdU *in vivo* provided that all S phase cells are exposed to (and able to transport and incorporate) sufficient labelled precursor into DNA to give an immunocytochemical stain (Gratzner, 1982; Hoshino *et al.*, 1985). If these conditions are met, the BrdU labelling index is equivalent to the S phase fraction. Moreover, fractionated exposure of a cell population to BrdU for the cell cycle time period is equivalent to the growth fraction (Yoshii *et al.*, 1986). We reported that measurement of the BrdU labelling index (S phase fraction) in urological cancer might provide an objective and quantitative new assay of biological potential in individual tumours (Nemoto *et al.*, 1988, 1989a and b). We now report the first studies using fractionated exposure to BrdU to determine the growth fraction of invasive bladder cancer.

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Patients and Methods

Tissue specimens from patients with transitional cell bladder cancer without any prior therapy were subjected to BrdU labelling. In accordance with the classification system of the International Union Against Cancer (UICC, 1978), tumours were described as T2 (tumour invading superficial muscle), T3 (tumour invading deep muscle) and T4 (tumour invading the membranes and surrounding tissue). Biopsies were graded according to the World Health Organization system (Mostofi *et al.*, 1973). To label the S phase fraction, patients received a 0.5-h intravenous infusion of bromodeoxyuridine (Radibud, Takeda Drug Co. Ltd, Osaka, Japan), 200 mg/mm^2, 2 to 3 h before transurethral resection and cold cup biopsy. Patients were eligible for selective intra-arterial chemotherapy and pelvic radiation before total cystectomy if they had a histologically proven high grade transitional cell carcinoma with muscle invasion. Bilateral catheters were placed into the internal iliac artery via the inferior gluteal artery for infusion of the anti-cancer drug. To estimate the growth fraction, patients received 150 mg fractionated labelled BrdU through these catheters every 6 to 10 h for 3 days before chemotherapy and radiation. Cold cup biopsy was done 2 to 3 h after the last infusion of BrdU. Informed consent was obtained from each patient prior to the procedure.

The biopsy specimens were fixed with 70% ethanol, embedded in paraffin, sectioned, and stained by an indirect immunoperoxidase method using anti-BrdU monoclonal antibody (Fujisawa Co., Osaka, Japan) as the first antibody. The tissue sections were denatured for 1 h in 2N-HCl, covered with 1:30 dilution of purified anti-BrdU monoclonal antibody in phosphate-buffered saline containing 0.5% Tween 20 and left at room temperature for 45 min. The slides were then incubated with a 1:200 dilution of peroxidase-conjugated anti-mouse immunoglobulin (Ig) G antibody in phosphate-buffered saline for 45 min at room temperature and then with 0.025% diaminobenzidine tetrahydrochloride and 0.003% H_2O_2 in Tris-HCl buffer for 10 to 15 min. Finally, the slides were lightly counterstained with 10% Gill haematoxylin. The remaining portion of each specimen was fixed in 10% formalin for routine histological examination.

Between 100 and 300 cells were counted in each of 3 to 8 microscopic fields from well labelled areas to determine the average S phase fraction and growth fraction; approximately 1000 cells were counted in each case. The mitotic index was not determined. The S phase fraction and growth fraction were expressed as the ratio of BrdU labelled cells to the total number of cells counted.

Results

The clinical stage and pathological diagnosis in 8 patients and the labelling index (S phase fraction and growth fraction) of their tumours are summarised in the Table. Sections of alcohol-fixed biopsy specimens, stained with immunoperoxidase for BrdU from patients with invasive bladder cancer, are shown in Figures 1 and 2. The immunoperoxidase staining for BrdU was confined to the nucleus and consisted of both punctate and diffuse patterns. There was an area which could not be stained with anti-BrdU monoclonal antibody around the stained area (Fig. 3). The growth fraction varied among tumours and between different areas. The areas of tumours scored were confined to the sections without microscopic necrosis and with fairly homogeneous labelling. The average S phase fraction of the invasive bladder cancer, calculated from tissue sections, was 18.0 ± 6.4% (mean ± SD, range 12.0–28.2%), while the average growth fraction from the same patients was 38.4 ± 7.7% (range

Table S Phase Fraction and Growth Fraction of Human Bladder Tumour *in situ* with Bromodeoxyuridine Labelling

Patient No. (Age, sex)	*Grade*	*TNM*	*S phase fraction (%)*		*Growth fraction (%)*	
			Mean ± SD	*Range*	*Mean ± SD*	*Range*
1 (79M)	2	T2N0M0	15.0 ± 4.3	8.9–20.3	35.7 ± 4.7	30.6–42.1
2 (71M)	2	T3N0M0	12.0 ± 3.1	8.6–14.8	30.4 ± 4.6	26.2–36.9
3 (75M)	2	T2N0M0	12.6 ± 2.9	9.2–15.5	26.9 ± 2.7	20.3–34.5
4 (86M)	3	T3N0M0	13.6 ± 2.6	11.7–16.6	41.4 ± 4.0	37.0–46.3
5 (55M)	3	T4N2M1	25.3 ± 4.4	19.8–34.0	43.8 ± 2.1	43.0–46.8
6 (61M)	3	T3N1M0	14.3 ± 5.2	8.4–18.8	34.3 ± 4.5	29.3–38.9
7 (56M)	3	T2N0M0	22.8 ± 1.9	20.7–25.4	46.4 ± 5.5	40.0–53.9
8 (79M)	3	T3N0M0	28.2 ± 4.1	24.9–33.8	48.1 ± 2.9	47.0–51.2

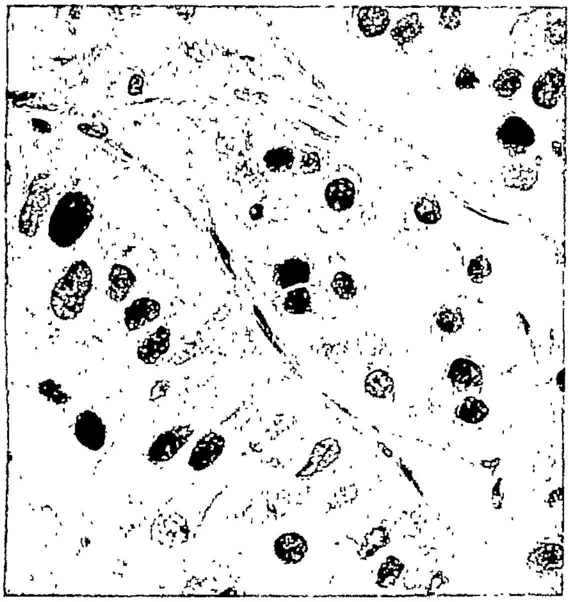

Fig. 1 Case 2. Grade 2 transitional cell carcinoma of urinary bladder. Section prepared with immunoperoxidase stain for BrdU after fractionated infusions of BrdU, showing several labelled (dark) nuclei among haematoxylin-stained (light) nuclei, counterstained with haematoxylin. (× 125). Percentage labelled cell indicates growth fraction.

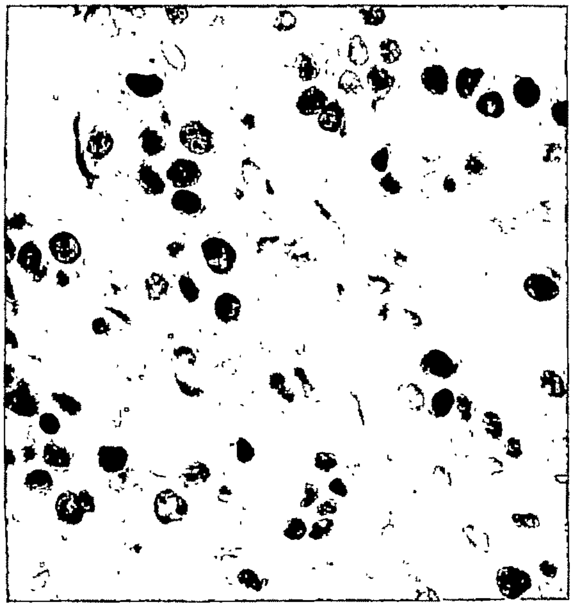

Fig. 2 Case 3. Grade 3 transitional cell carcinoma of urinary bladder. Section prepared with immunoperoxidase stain for BrdU after fractionated infusions of BrdU, counterstained with haematoxylin. (× 125).

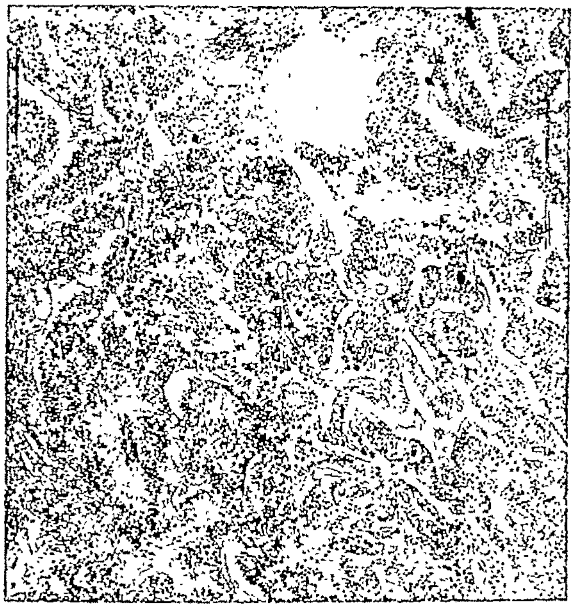

Fig. 3 Case 2. Grade 2 transitional cell carcinoma of urinary bladder. Immunoperoxidase stain for fractionated labelling with BrdU shows islands which could not be stained with anti-BrdU monoclonal antibody. (× 20).

26.9–48.1%). Grade 3 tumours (5 cases) averaged 42.8 ± 5.4 labelling versus $31.0 \pm 4.4\%$ in grade 2 tumours (3 cases). A high number of BrdU positive cells was found in tumours with high histological grade.

When 8 values of growth fraction were plotted against the corresponding S phase fraction, there appeared to be a linear correlation. Linear least squares analysis gave an intercept point of 19.8, a slope of 1.0 and a high correlation coefficient (R) (0.86).

$$\text{Growth fraction} = 19.8 + 1.0 \times (\text{S phase fraction})$$

Alternatively, when the growth fraction was sought as a power function of S phase function, the fit also appeared to be good (Fig. 4).

$$\text{Growth fraction} = 8.53 \times (\text{S phase fraction})^{0.52} \quad (R = 0.85)$$

Discussion

Several methods are currently available for determining growth fraction. However, ethical considerations, as well as the radiation hazards involved, limit the investigations that may be performed on patients with fractionated labelling using ^{3}H-

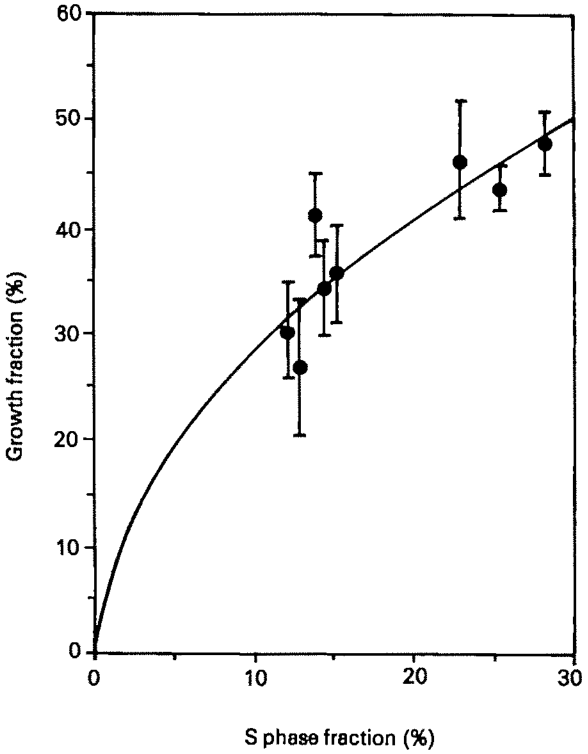

Fig. 4 Growth fraction plotted against S phase fraction. Points represent values and bar = standard deviation.

thymidine. The method used here appears to be the only means at present of determining these important cell kinetic parameters in patients with bladder cancer.

BrdU has been administered as a radiosensitising agent to patients with malignant tumours of the brain, head and neck at an intra-arterial dose of 500 to 1000 mg/day for 4 to 6 weeks without serious side effects (Bagshaw *et al.*, 1967; Hoshino and Sano, 1969; Mitchell *et al.*, 1983; Russo *et al.*, 1984). Daily intravenous infusions of BrdU, 600–700 mg/ml^2, for several weeks can be tolerated without severe myelosuppression (Mitchell *et al.*, 1983). Intravenous administration of BrdU should be limited to less than 700 mg/m^2/day in order to prevent myelosuppression (Mitchell, 1983). A fractionated infusion with BrdU through the intra-arterial catheter was performed in this study to suppress the total dose of drugs to under 500 mg/day.

The dose schedule used in the present series was selected because the expected duration of the S phase in most poorly differentiated malignant tumours is 6 to 20 h and the cell cycle is 1 to 3 days (Meyer, 1981). We therefore administered 150 mg BrdU in an intra-arterial pulse infusion every 8 h for 3 days before biopsy in patients with advanced bladder cancer. The growth fractions determined by this method were very high in advanced bladder cancer. These results confirm that the fast growing tumours contain a large population of proliferating cells. In addition, growth fractions of bladder cancer in this study were similar to those in other types of poorly malignant tumours (Meyer, 1981).

There was an area surrounding stained areas which could not be stained with anti-BrdU monoclonal antibody. In several sections the labelling pattern showed labelled islets surrounded by unlabelled epithelial zones where diffusion effects could be excluded. The growth fraction varied widely among tumours and between different areas from the same tumour. This indicates a growth fraction <1 and implies that only a proportion of the tumour cells in bladder tumours are cycling and contributing to growth. In experimental tumours, growth zones are not randomly distributed (Denekamp and Kallman, 1973). This has also been shown in selected human tumours (Lieb and Lisco, 1966). Proliferative kinetics, growth fraction and cell loss are dependent on vascularisation (Tannock, 1968). Transplantation experiments and *in vitro* models revealed the importance of the microenvironment to which different parts of the tumour are exposed (Broyn, 1975) and showed the dependence of the proliferative pattern on tumour geometry (Broyn, 1975), nutrition and oxygenation (Tannock, 1968). The non-proliferative pool has important therapeutic implications since this fraction of the population is less sensitive to radiation or chemotherapy and is probably responsible for eventual relapse following treatment. An investigation of the whole tumour appears necessary for an evaluation of the proliferative state of human bladder cancer.

It may be said that the growth fraction of non-invasive G1 tumours must be evaluated to estimate the statistical curve, in practice this is almost impossible. Theoretically, in slow growing G1 tumours, BrdU must be infused for more than 10 days in order to label all cycling cells and estimate the growth fraction (Meyer, 1981). Moreover, patients with non-invasive G1 tumours are not suitable for selective arterial infusion of anti-cancer drugs. There is no method of selectively labelling cells with low doses of BrdU over long periods of time in these tumours.

Although the present series was small and only invasive G2–G3 tumours were studied, the growth fraction correlated reasonably well with the S phase fraction. Two equations were proposed in order to delineate the relationship between these 2 parameters. A linear least squares analysis fits well but fails in the area of lower S phase fraction values because a tissue that shows a labelling index=0% should have a growth fraction of 0%. A power function also fits well, although interpretation of this equation is difficult (Hoshino and Wilson, 1979). A tumour that has a critical S phase fraction of 10% and a poor prognosis (Nemoto *et al.*, 1988) may have a growth fraction of 25%. A well differentiated bladder tumour with a labelling index <2% may show a growth fraction <10%. It is evident that determination of the growth fraction is necessary to understanding the true potential proliferative activity of a given tumour. As might be expected, studies involving continuous or fractionated infusion of BrdU are inconvenient and time-consuming for patients with bladder tumours. Our results reveal that the growth fraction, as determined by fractionated infusions of BrdU, correlates reasonably well with the S phase fraction determined by pulse infusion. The S phase fraction would be a preferable practical measure for the estimation of biological malignancy in bladder tumours (Nemoto *et al.*, 1988).

Our experience in this small series suggests that this method can help to increase knowledge of the biological properties of tumours and can form a valuable supplement when assessing and treating patients with bladder tumours. A definitive evaluation of the technique can be made only by studying a larger number of patients.

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Long-term Follow-up of Intravesical Epodyl Therapy for Superficial Bladder Cancer

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Summary—The records of 111 patients with multiple superficial grade 1–2 transitional cell tumours of the bladder treated with intravesical Epodyl and followed up for a mean period of 6.4 years were retrospectively analysed. The study showed that 65% of patients responded completely after 12 weekly instillations and 46% of these remained continuously free of disease for 5 years. An initial complete response to therapy and lower pathological grade seemed to indicate a long-term successful response to treatment. In patients who failed to respond by 1 year, further therapy was of no benefit. Clearance of bladder disease by 1 year carried a 14% risk of subsequent tumour invasion by 5 years. This risk increased to 75% in those who failed to respond by 1 year.

Many patients with multiple superficial transitional cell tumours of the bladder require intravesical chemotherapy if endoscopic measures fail to control the disease. Of the many chemotherapeutic agents available, Epodyl (triethylene glycol diglyceridyl ether) has been in use for over 2 decades. It is an alkylating agent, poorly absorbed through the bladder mucosa owing to its higher molecular weight, and therefore carries a lesser risk of systemic toxicity (Abbassian and Wallace, 1966; Riddle and Wallace, 1971). Nonetheless, it has not achieved worldwide popularity in the management of superficial bladder cancer, which is reflected by the relatively small number of long-term studies on this subject. Most of the reports on Epodyl and indeed on the whole subject of intravesical chemotherapy have tumour recurrences as their end point. Radical treatment is then frequently employed. This prevents one ascertaining the true incidence of tumour invasion over the longer term.

We report a retrospective study on 111 patients with multiple superficial transitional cell tumours of the bladder who received intravesical chemotherapy with Epodyl and were followed up for a maximum of 11 years. It was departmental policy to embark on radical treatment only in the event of tumour invasion. The aims of the study were to assess the usefulness of Epodyl in the management of superficial bladder cancer, to identify factors which might influence the ultimate success or failure of treatment and to analyse the incidence of tumour invasion in the long term.

Patients and Methods

During the period 1975 to 1985, 111 patients with recurrent multiple, grade 1–2, stage T_a–T_1 transitional cell tumours of the bladder uncontrolled by conventional endoscopic methods were treated with intravesical Epodyl. The series comprised of 97 males and 32 females (age range 38–78 years, mean 62). The mean follow-up was 6.4 years.

Treatment was started 2 to 4 weeks after complete clearance of tumours by endoscopic resection and/or diathermy to allow the bladder to epithelialise, and was administered weekly or monthly on an outpatient basis. Prior to each instillation, the urine was sent for bacteriological examination. The bladder was emptied by catheterisation with an 8 F Jacques catheter and 100 ml of a freshly prepared 1% solution of Epodyl instilled into the bladder. The patients retained the solution for as long as possible, up to a maximum of 2 h. They were ambulatory during this period. Treatment was withheld if the previous urine result revealed the

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Read at the 44th Annual Meeting of the British Association of Urological Surgeons in Buxton, June 1988

presence of infection and resumed only after it was eradicated by appropriate antimicrobial therapy. Treatment was also interrupted if the patient developed symptoms of chemical cystitis and recommenced after improvement in symptoms.

Regimen (Fig. 1)

All patients had 12 weekly instillations (Course 1). The interval between the instillations was increased if the patient developed bacterial or chemical cystitis. Patients with no evidence of recurrent tumours on the first cystoscopic evaluation after completing Course 1 had no further treatment. Those showing definite improvement (characterised by a decrease in the number and size of the tumours compared with the pre-treatment cystoscopy) and those with no response received a further course of 12 monthly instillations (Course II). Those who were tumour-free on cystoscopy after the completion of Course II received no more.

Partial or non-responders to Course II were given 12 more monthly instillations (Course III). Those with persistent recurrences even after 36 successive instillations were classed as non-responders and treatment was discontinued.

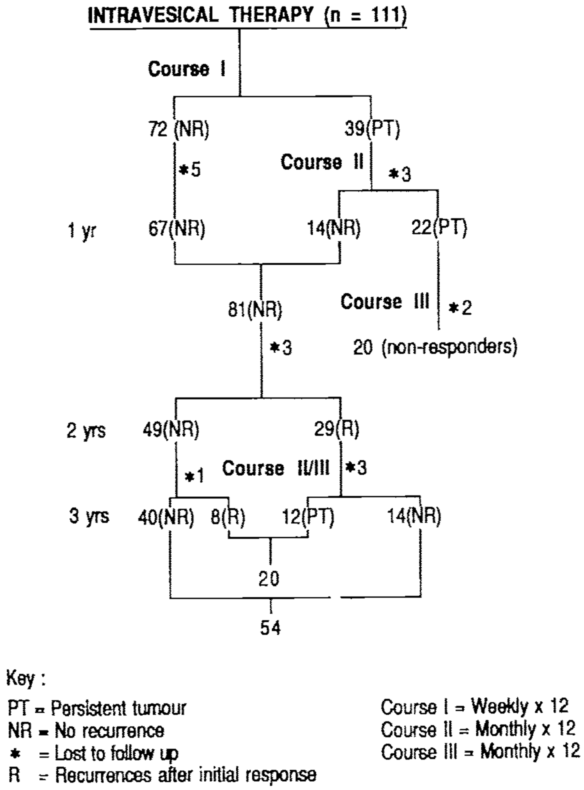

Fig. 1 Therapeutic regimen and response.

Patients who responded completely after Course 1 or consecutive Courses 1 and 2 were followed up by regular cystoscopies. They received further therapy on a monthly basis if they developed recurrent tumours at any stage during follow-up.

The life table method using BMDP Program PIL was used to analyse the incidence of freedom from disease and the incidence of tumour invasion in various subgroups (Dixon *et al.*, 1985).

Results

Overall response to treatment (Fig. 1)

Of the 111 patients, 72 (65%) showed no recurrences at the first endoscopic assessment following completion of Course 1. The 39 partial or non-responders received a second course of 12 monthly instillations; 36 of these patients completed the course, by which time 14 (39%) were tumour-free. At the end of 1 year, 81 patients (73%) were tumour-free; 94 patients were available for follow-up at 3 years and 54 of these (57%) were free of disease.

Of 22 patients who continued to have multiple recurrences after courses I and II, 20 completed 12 further monthly instillations (Course III). None responded. The pre-therapy tumour histology was grade 1 in 3 patients (15%) and grade 2 in 17 (85%). Of the 54 patients who were free of disease at 3 years, the pre-therapy tumour histology was grade 1 in 32 (59%) and grade 2 in 22 (41%) (Table 1). The comparison between the 2 groups was statistically significant ($P<0.001$).

Freedom from disease

After Course I (12 weekly instillations). After 12 weekly instillations alone, 72 patients were tumour-free (Fig. 1). Of these, 46% remained continuously tumour-free for 5 years (Fig. 2).

Table 1 Influence of Tumour Grade on Response

	No. of patients	*Histological grade*	
		G1 (%)	*G2 (%)*
No response after 36 consecutive instillations	20	3* (15)	17* (85)
Disease-free 3 years after 1 or more courses	54	32* (59)	22* (41)
Previous complete response but disease present at 3 years	20	13 (65)	7 (35)

$^*P<0.001$

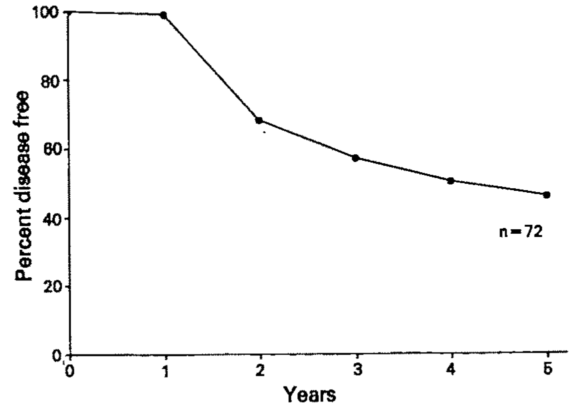

Fig. 2 Actuarial percentage of patients continuously free of disease after 12 weekly instillations.

After Course II (12 weekly and 12 monthly instillations). Of the 14 patients who responded to Course II after failure to respond to Course I, 16% remained continuously free of disease for 5 years (Fig. 3).

Sequelae

A total of 2389 catheterisations were performed on 111 patients and 26 urinary tract infections were documented (1%). Symptoms of chemical cystitis were reported only by patients receiving weekly instillations and the overall incidence was 19%. Symptoms were controlled by increasing the interval between the instillations.

Freedom from invasion

The incidence of freedom from invasion at 5 years was 86% in patients disease-free at 1 year (n=81) but only 25% in those having persistent tumour at 1 year (n=22) (Fig. 4).

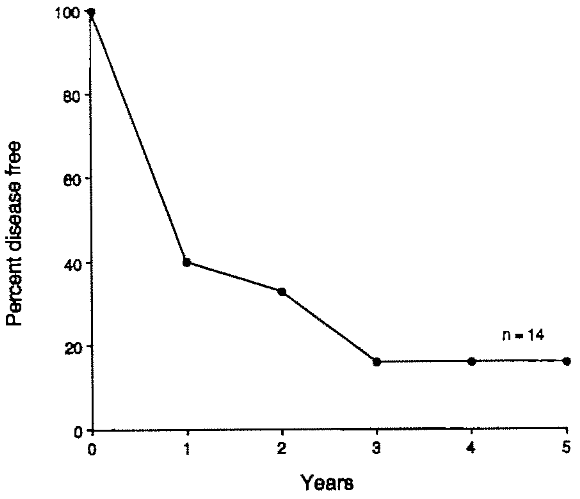

Fig. 3 Actuarial percentage of patients continuously free of disease after 12 weekly and 12 monthly consecutive instillations.

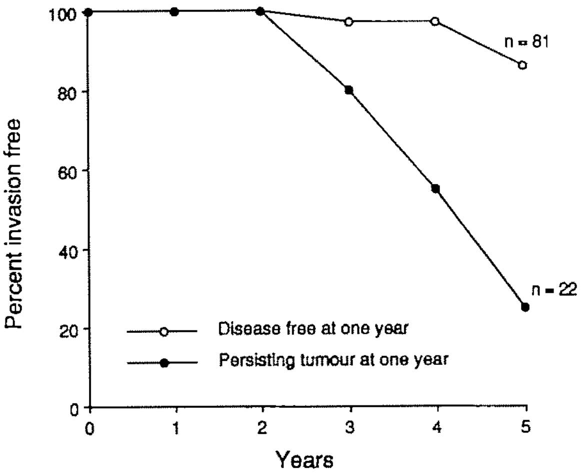

Fig. 4 Freedom from invasion: comparison between patients disease-free at 1 year and those with persistent tumour at 1 year.

Discussion

The overall response rate of 73% at 1 year in this study corroborates the results of other studies (Table 2) (Fitzpatrick *et al.*, 1979; Nielson and Thybo, 1979; Colleen *et al.*, 1980; Riddle *et al.*, 1982). With large numbers and a long follow-up period, the results of this study showed that the best indicator of success was the initial response to 12 weekly instillations of Epodyl; 72 patients responded to Course I, of whom 46% remained free of tumour for 5 years (Fig. 2).

In the event of lack of response to 12 weekly instillations, a further 12 monthly instillations were useful but the response was not long-lasting. After failing to respond to Course I, 36 patients completed Course II and 14 (39%) responded. However, of these 14 patients only 16% remained tumour-free for 5 years (Fig. 3).

Table 2 Intravesical Epodyl Treatment and Early Response

Author	*No. of Patients*	*Complete response No.*	*(%)*
Nielson and Thybo (1979)	36	23	(64)
Fitzpatrick *et al.* (1979)	64	39	(61)
Colleen *et al.* (1980)	29	23	(79)
Riddle *et al.* (1982)	139	70	(50)
Present series	111	81	(73)

If the tumours continued to recur after 24 consecutive instillations, further Epodyl therapy was of no benefit. In retrospect, it seems that the treatment was continued for longer than necessary in 20 patients who received 3 consecutive courses.

Pre-therapy tumour grade was significantly related to the response, with grade 2 tumours less likely to respond (Table 1).

A patient with multiple bladder tumours which have not cleared after 1 year's treatment with Epodyl has a 75% chance of developing tumour invasion within 5 years (Fig. 4). Elective radical surgery appears to be mandatory in such a case.

Clearance of bladder disease by 1 year carries a subsequent risk of invasive disease of only 14% (Fig. 4). A policy of regular reviews, early drug treatment of recurrences and cystectomy only in the event of lack of response can be justified in this group.

The reason why Epodyl has not achieved popularity is possibly due to the reported incidence of chemical cystitis, which has ranged from 8 to 25% (Robinson *et al.*, 1977; Smith *et al.*, 1978; Nielson and Thybo, 1979; Fitzpatrick *et al.*, 1979; Colleen *et al.*, 1980). In this study, 19% of patients developed symptoms of chemical cystitis severe enough to interrupt treatment. However, increasing the interval between instillations helped to alleviate the symptoms and allowed the treatment to be continued. This problem was not encountered in patients receiving monthly instillations.

In summary, the present study has shown that Epodyl has a definite place in the management of multiple superficial bladder tumours. It is cost effective, suitable for use in out-patient clinics and has no systemic toxicity. An initial complete response to therapy and a lower pathological tumour grade appear to indicate a long-term successful response. In patients who fail to respond by 1 year, further therapy offers no benefit and radical surgery should be given serious consideration. In those who do respond, careful supervision is necessary to achieve the best results over the longer term.

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Multicentre Controlled Trial of Indoramin in the Symptomatic Relief of Benign Prostatic Hypertrophy

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Summary—A group of 139 patients with symptoms of bladder outflow obstruction due to benign prostatic hypertrophy were entered into a double-blind, parallel group, multicentre study of 2 doses of indoramin versus placebo. There were 18 withdrawals or exclusions, leaving 121 patients for analysis.

After 8 weeks, mean peak flow rates increased more in patients treated with indoramin 20 mg *bd* than in those with placebo. The difference between indoramin 20 mg *nocte* and placebo was not significant. The change in mean peak flow rate for the higher dose of indoramin represented an increase of 50%. Both patients and investigators reported that the patients' symptoms had improved significantly on both indoramin 20 mg *bd* and 20 mg *nocte*; 9 patients were withdrawn because of adverse events, 5 taking placebo and 2 in each of the treatment groups.

It was concluded that indoramin 20 mg *bd* was both effective and well tolerated in the management of symptomatic benign prostatic hypertrophy.

Prostatic hypertrophy with symptoms of urinary outflow obstruction is a common disease of ageing males. Prostatectomy is the treatment of choice but Caine *et al.* (1976) reported that alpha-adrenergic receptor antagonists can assist in management by easing the symptoms of outflow obstruction.

Indoramin is a competitive alpha$_1$-adrenoceptor antagonist with no β-blocking or anticholingergic activities. As it appears that the stimulation of α-adrenoceptors contributes to the obstruction of benign prostatic hypertrophy (Caine *et al.*, 1976), blockade with indoramin ought to be effective therapeutically. An earlier pilot study using doses between 50 and 100mg daily (Iacovou and Dunn, 1987) suggests that this is true.

We present a study which evaluated the effect of lower doses of indoramin (40 or 20 mg daily) on urinary flow rates and symptoms in patients with benign prostatic hypertrophy.

Patients and Methods

This double-blind, placebo-controlled, parallel group study was conducted in urology out-patient clinics at 13 hospitals from December 1986 to January 1988.

Patients suffering from benign prostatic hypertrophy who fulfilled the conditions of entry (Table 1) underwent urinary flow rate measurements. Pulse and blood pressure were recorded and symptoms assessed. Patients were randomly allocated to 3 groups to receive either placebo or indoramin at a dose of 20 mg *nocte* or 20 mg *bd.* They returned after 4 and 8 weeks of treatment, when all of the assessments made at entry were repeated. At the final visit a single assessment on a 5-point scale of the change in symptoms was made by both the patient and the surgeon.

Table 1 Conditions of Entry

Males over 45 years with symptoms of bladder outflow obstruction
Clinical diagnosis of benign prostatic hypertrophy
Objective evidence of diminished urine flow
No significant cardiovascular disease
No significant renal and/or hepatic disease
No depression
No extrapyramidal disorder
No neurogenic bladder, multiple sclerosis, spinal injury
No antihypertensives (except diuretics), MAOIs, cholinergics or anti-cholinergics

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The study group comprised 139 men. Their ages ranged from 46 to 84 years (mean 64); 47 were assigned to placebo, 47 to indoramin 20 mg *nocte* and 45 to indoramin 20 mg *bd*; 18 were excluded from the analysis (6 defaulted, 6 were withdrawn before the week 4 visit, 6 violated the protocol); therefore 121 patients were included in the efficacy analysis, of whom 43 received indoramin 20 mg *nocte*, 38 received indoramin 20 mg *bd* and 40 received placebo.

Statistical analysis

Demographic characteristics were compared using the chi-squared test to compare treatment groups and an analysis of variance to compare the treatment groups with respect to age. The changes in peak flow rate, voiding time and voiding volume were analysed separately, comparing the change from baseline using the paired *t*-test. A chi-squared test was used to compare the treatment for both doctor's and patient's assessment of change.

Results

These are summarised in Table 2. After 8 weeks there was a significant increase from baseline in peak urinary flow rate of 4.9 ml/s (59.0%) in the indoramin 20 mg *bd* group ($P<0.01$), 2.8 ml/s (26.9%) in the indoramin 20 mg *nocte* group ($P<0.05$) and 1.8 ml/s (16.5%) in the placebo group (NS). The difference between indoramin 20 mg *bd* and placebo was significant ($0.05<P<0.10$) (Fig.)

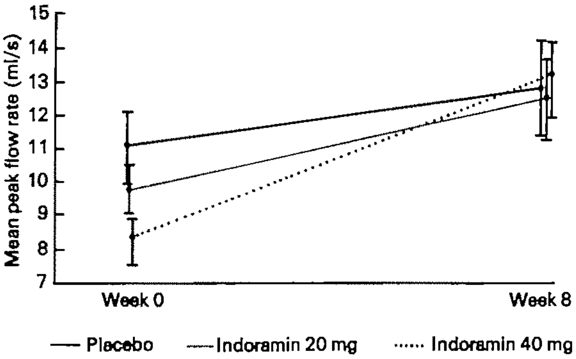

Fig. Mean peak flow rate (ml/s) for patients with week 8 visits. Bars represent 1 standard error either side of the mean.

The effects on voiding time and voided volume were small in all 3 treatment groups, with no significant difference between them. With regard to symptomatic improvement, 78% of patients taking the higher dose of indoramin reported that their symptoms had either improved or resolved compared with 64% of those taking indoramin 20 mg *nocte* and 53% taking placebo; the difference between indoramin 20 mg *bd* and placebo was statistically significant ($P<0.05$). This greater symptomatic improvement on indoramin was reflected in the doctor's assessment of the change in the patient's condition. Symptoms improved in 38% of the placebo-treated group compared with 63% in the indoramin 20 mg *nocte* group ($P<0.05$) and 76% in the indoramin 20 mg *bd* group ($P>0.01$).

Nine patients were withdrawn because of adverse events (Table 3). No consistent effect on blood pressure was evident in any of the treatment groups and there was no evidence of a hypotensive effect in the indoramin-treated patients.

Discussion

Several controlled studies have demonstrated both objective improvement of obstruction and relief of symptoms in patients with benign prostatic hyper-

Table 2 Change from Baseline at 8 Weeks in Peak Flow Rate, Voiding Time and Voiding Volume

	Peak flow rate (ml/s)			*Voiding time (s)*			*Voiding volume (ml)*		
	P	*120*	*140*	*P*	*120*	*140*	*P*	*120*	*140*
Mean at baseline*	11.07	9.76	8.28	61.65	60.99	66.43	225.02	249.58	187.25
Mean at 8 weeks*	12.82	12.54	13.18	48.12	50.26	51.74	243.61	220.36	224.81
Difference in means	1.75	2.79	4.90	−13.53	−10.73	−14.69	18.59	−29.22	37.56
No. of patients	34	39	37	31	31	32	34	39	37
95% confidence interval for difference in means	(−0.67, 4.17)	(0.53,5.05)	(2.58,7.22)	(−25.41, −1.65)	(−22.61, 1.15)	(−26.39, −2.99)	(−31.71, 68.89)	(−76.18, 17.14)	(−10.66, 85.78)
P	NS	<0.05	<0.01	<0.05	0.05<*P* <0.10	<0.05	NS	NS	NS

P = Placebo
120 = Indoramin 20 mg/day
140 = Indoramin 40 mg/day
* Means based on patients with both baseline and week 8 assessments.

Table 3 Withdrawals due to Adverse Events

- Placebo (5 patients)
  - Epigastric pain
  - Agitation, anxiety, palpitations
  - Worsening symptoms of BPH
  - Bone and joint pains
  - Urinary tract infection
- Indoramin 20 mg nocte (2 patients)
  - Sweating, stomach cramps, chest pain, impotence
  - Headaches
- Indoramin 20 mg *bd* (2 patients)
  - Depression
  - Indigestion, weak limbs, joint strain

trophy during treatment with α-adrenoceptor antagonists. Phenoxybenzamine, a non-selective, α-adrenoceptor antagonist, was the first to be used to treat benign prostatic hypertrophy, and improved both urinary flow rate and frequency of micturition in controlled trials (Caine *et al.*, 1981; Abrams *et al.*, 1982). However, it produced side effects in about 30% of patients, necessitating withdrawal of treatment in 10%.

More recently prazosin, a selective α_1-antagonist, has been investigated and controlled trials have confirmed its efficacy in the treatment of benign prostatic hypertrophy (Hedlund *et al.*, 1983; Kirby *et al.*, 1987).

A preliminary study by Iacovou and Dunn (1987), using doses of indoramin between 50 and 100 mg daily, produced significant relief of symptoms and improved peak urinary flow rates. Another recently completed study (Stott and Abrams, 1988) demonstrated increased urinary peak flow rates and decreased nocturia at a well tolerated lower dose of 20 mg twice daily.

The results of the present study suggest that treatment with indoramin significantly improved peak flow rates over an 8-week period. The 5 ml/s mean increase in peak flow rates observed in patients treated with 20 mg twice daily, a dose less than the minimum recommended for indoramin in the management of hypertension (Baratol prescribing information, Wyeth), represents a substantial improvement of more than 50%. This is of the same order as the improvement seen by Susset and Dutartre (1975) following prostatectomy.

Both patients and investigators reported that indoramin relieved symptoms significantly better than placebo, with the higher dose producing the better response. The number of adverse events was similar in the 3 groups, although there was a higher incidence of events possibly attributable to alpha-blockade in the indoramin-treated groups.

The results indicate that indoramin is both effective and well tolerated in the treatment of symptomatic benign prostatic hypertrophy, with the higher dose of 20 mg twice daily producing the better result.

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Extravascular Absorption of Irrigating Fluid during TURP. The Role of Transmural Bladder Pressure as the Driving Pressure Gradient

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Summary—The critical intravesical pressure range for extravascular absorption of irrigating fluid (EVA) during transurethral resection of the prostate (TURP) is determined by the pressure in the perivesical tissue. This means that the transmural bladder pressure (detrusor pressure), calculated by deducting perivesical pressure from intravesical pressure during cystometry, is the pressure gradient behind EVA. The transmural pressure in 6 patients undergoing TURP has been studied both before and during epidural anaesthesia, using both conventional medium-fast fill cystometry and "free-flow" cystometry through the resectoscope. Epidural block does not influence the transmural pressure response on filling the bladder and neither does the type of infusion. A positive transmural pressure, and thereby a pressure gradient for EVA, exists already during the very early phase of bladder filling. Incomplete perforation of the prostatic capsule and clotting, as well as the accumulation of irrigating fluid in the perivesical tissue, probably moderate the rate of absorption.

As long as the aim of the surgeon performing transurethral resection of the prostate is to visualise completely the prostatic capsule, he will eventually face the first of the 2 prerequisites for irrigating fluid absorption; open veins and/or perforations of the capsule. Secondly, a pressure head which drives the solution into the veins (intravenous absorption, IVA) or through the capsular perforations into the surrounding tissue (extravascular absorption, EVA), is always close at hand.

Once fluid is in the operating area, the critical pressure for IVA is the pressure in the prostatic (or pelvic) veins (Hultén *et al.*, 1984a). Although it has been calculated that as much as two-thirds of the absorbed volume infiltrates the perivesical tissue as EVA (Oester and Madsen, 1969), the pressure conditions which induce this process have not yet been investigated. Theoretically, the critical intravesical pressure range is determined by the pressure in the surrounding tissue. However, none of the reports on irrigating fluid absorption discusses the magnitude or duration of this pressure. Hahn *et al.* (1987), studying the intravesical pressure during irrigating fluid absorption, found that EVA could occur at lower pressures than IVA, and their results indicated that irrigating fluid entered the perivesical space at a lower critical pressure than it did when entering the circulating blood.

The prevesical, perivesical and periprostatic spaces are intercommunicating areas within the same anatomical compartment. The pressure within this compartment is influenced by the pressure exerted by the joint cavities of the bladder and the prostatic fossa (operating field). Once again, the main factor governing compliance is the bladder wall itself rather than the stiff, non-compliant residual prostatic tissue and capsule.

In cystometry, both intravesical and perivesical pressure are monitored in order to calculate the detrusor pressure—or the transmural bladder pressure—by subtracting the perivesical from the intravesical pressure (Bjerle, 1974). We believe that this transmural bladder pressure is identical to the excessive pressure in the bladder necessary for EVA.

However, the basic work on transmural bladder

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pressure by Bjerle (1974) was confined to bladder volumes below 300 ml in healthy young volunteers; no anaesthetics were used and the filling rate was 50 ml/min, circumstances very different from those found during TURP.

Intravesical pressure (and its relation to the pressure in the pelvic veins) in the decentralised bladder has already been studied (Hultén *et al.*, 1984b; Hultén and Hjertberg, 1984), but the changes in transmural pressure under the same conditions have yet to be described.

Patients and Methods

Six patients with prostatic hypertrophy who were scheduled for TURP were studied; all gave informed consent. They were otherwise healthy, with no history of bladder decompensation and no urinary infection at the time of operation. None used drugs with possible effects on the lower urinary tract.

Continuous medium-fast fill cystometry (50 ml/min) was performed with the 6 patients in the lithotomy position (group A), using a standard technique (Bjerle, 1974). This involved 2 catheters inserted percutaneously into the bladder by suprapubic puncture, 1 for infusion and 1 for recording intravesical pressure. A third catheter was passed by the same route, but the tip remained just outside the bladder wall in order to monitor perivesical pressure.

Thereafter, the patients were transferred to the operating theatre where they underwent a combined, continuous lumbar and sacral epidural block. Analgesia below the fifth thoracic segment was maintained by injecting mepivacaine (1%) through catheters (Hultén *et al.*, 1984b).

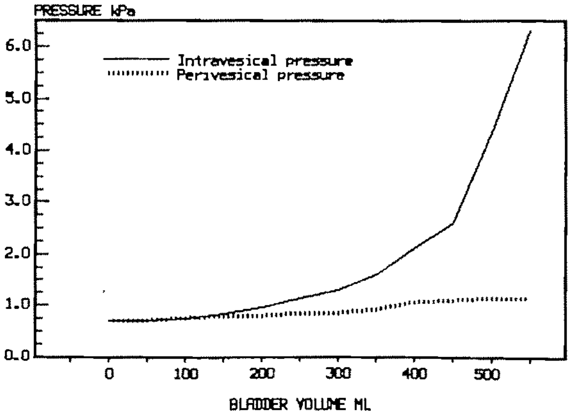

Fig. 1 Medium-fast fill cystometry during epidural anaesthesia with the patient in the position for TURP. 0 level = symphysis.

Medium-fast fill cystometry was repeated in 5 patients (group B). In 1 case the prevesical catheter failed to work and was replaced by another catheter, introduced along the perineal route through a long needle. This was guided by one finger in the rectum and the tip of the catheter placed dorsal to the prostate and slightly lateral to the right lobe. An example of the readings obtained in 1 patient is given in Figure 1.

Finally, in 4 patients (group C), including the one with the replaced perivesical catheter, a "free-flow" cystometry was performed by infusing glycine (2.2%) from a bag (Uromatic, Travenol) through a resectoscope (Storz, 24 F) with the stop-cock fully open. The bag was placed with its centre about 60 cm above the bladder. During this type of cystometry the fluid flow rate was derived from the continuously recorded weight loss of the bag.

Cystometries without analgesia were continued until the patients complained of discomfort. The same procedures, using epidural block, were terminated when the intravesical pressure rose sharply. Spontaneous leaking of fluid from the urethra invariably occurred during filling and necessitated clamping of the urethra. "Free-flow" cystometry slows down automatically and stops as the intravesical pressure approaches that of the driving head.

The transmural pressure is calculated by deducting perivesical from intravesical pressure. The volume at bladder capacity during cystometry without analgesia is designated 100%. The transmural pressure is read at the end of every 10% increment of bladder volume and the mean values for each increment plotted to make up comparable curves for the 3 types of cystometry. A few bladders were filled relatively more than others during epidural analgesia, but only those increments shared by all of the individuals in the groups are shown in Figure 2.

Results

The transmural pressure was zero, or very close to zero, when the bladder was empty, both before and during epidural block.

During medium-fast fill cystometry (constant flow: 50 ml/min) the transmural pressure rose early but slowly. The curve recorded during analgesia was, however, almost identical with the curve obtained before the epidural block, except that the decentralised bladder was filled to a larger volume at a higher pressure level (Fig. 2).

The increase in transmural pressure in the

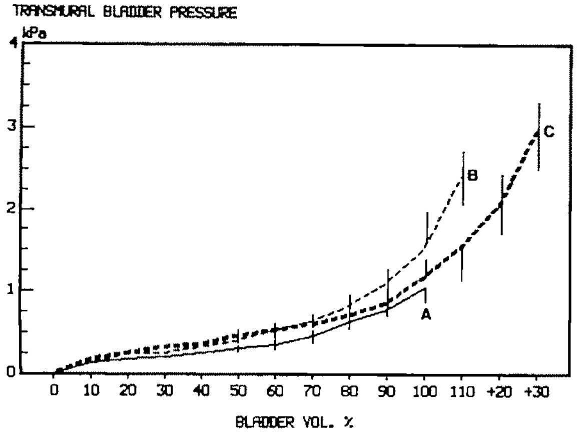

Fig. 2 Transmural bladder pressure. Group A (n=6): medium-fast fill cystometry (50 ml/min); Group B (n=5): medium-fast fill cystometry during epidural block; Group C (n=4): "free-flow" cystometry during epidural block. Volume increments in % of bladder capacity before anaesthesia.

individual bladder on filling followed a similar curve, regardless of whether the filling rate was a constant 50 ml/min or was established as a 'free-flow' flow cystometry through the resectoscope (Fig. 2). In the latter situation, the flow closely reflected the intravesical pressure (Fig. 3).

In 1 case where the perivesical pressure was measured through the suprapubic as well as the perineal route, the resulting transmural pressure obtained during conventional cystometry before analgesia corresponded completely with that obtained during "free-flow" cystometry.

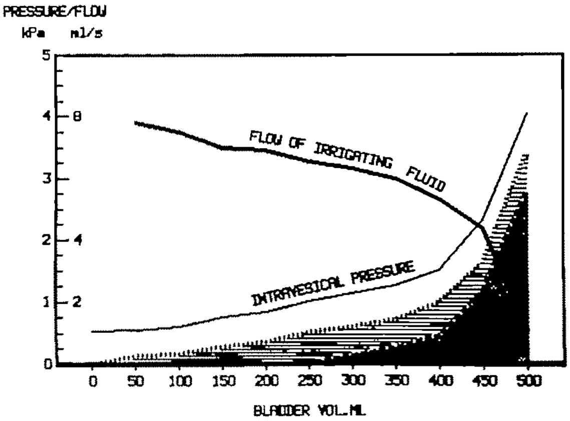

Fig. 3 Example of the pressure situation during bladder filling through the resectoscope. Total shaded area = pressure gradient for EVA. Darkest shaded area = pressure gradient for IVA. 0 level = prostatic urethra.

Discussion

Extravascular absorption is a complex process. The shift of fluid occurs through capsular perforations and is more or less counteracted by clogging of the perforations either by fat or—as the operation proceeds—by clot formation. Furthermore, the accumulation of irrigating fluid in the relatively demarcated perivesical space will discourage further absorption by raising the critical pressure range. To understand the basic mechanism of EVA we must disregard the effects of clogging, clotting and fluid accumulation.

The pressure in the operating field is identical to the intravesical pressure. Its behaviour during TURP, and especially its role in intravenous absorption of irrigant, has been investigated in detail by Hultén *et al.* (1984a).

Perivesical pressure, as a factor necessary to determine transmural bladder pressure, is well documented in the literature on cystometry (Nyman and Sjöberg, 1981; Bjerle, 1974) and leaves no doubt that both intravesical and perivesical pressures are involved in EVA.

Bjerle (1974) concluded that perivesical pressure, as monitored outside the bladder wall behind the symphysis, was truly representative of perivesical pressure. This is supported by our finding, in 1 patient, of no difference in the resulting transmural pressure when the pressure was monitored both in the space of Retzius and outside the dorsolateral aspect of the prostate. Transmural bladder pressure, measured by deducting the prevesical from the intravesical pressure, therefore represents the pressure gradient that governs EVA.

From this point of view, it is important to know that the transmural pressure is zero—or close to zero—only when the bladder is empty. It becomes positive early during the filling phase of the bladder, although it rises to high levels relatively late and in an individual fashion. This implies that, provided there is a perforation of the prostatic capsule, a low grade EVA may start early and need not wait until the intravesical pressure reaches the level of the pressure in the prostatic veins, as is required for IVA (Fig. 3). Figure 3 is based on the finding that during TURP in regional block anaesthesia and with the patient in the horizontal position, the intravesical pressure is lower than the pressure in the iliac vein until the bladder is filled to approximately 50% of its maximum volume at 4 kPa (Hultén and Hjertberg, 1984). The pressure in the prostatic veins is 0.2 to 0.3 kPa higher than the pressure in the iliac veins (Hultén *et al.*, 1984a).

On the other hand, the relatively low pressure gradient in the filling phase of the bladder causes a moderate EVA that may be counteracted if the perforation is blocked. A rising perivesical pressure, caused by accumulation of irrigating fluid in the tissue, should further reduce the pressure gradient. This explains the well-known fact that the most massive (and dangerous) EVA will arise when there is an open perforation of the bladder wall into the peritoneal cavity: no clotting will seal off such an opening and the intraperitoneal pressure will not rise to counteract the intravesical pressure.

It is interesting to note that the transmural pressure curve does not appear to be influenced by epidural analgesia. This also holds true for intravesical pressure (Hultén *et al.*, 1984b). The decentralised bladder may be filled to a larger volume than before only by reaching a higher pressure.

During epidural block the filling rate has no effect on transmural pressure: medium-fast filling evokes the same transmural pressure response as filling with "free-flow" through the fully open resectoscope. This is in accordance with previous findings on intravesical pressure during spinal block (Hultén and Hjertberg, 1984).

When IVA occurs, the bladder has been compared to a "punctured balloon", a metaphor that explains why, using intermittent irrigation, the maximum intravesical pressure during periods of IVA is significantly lower (and the filling cycles longer) than during periods of no absorption (Hahn *et al.*, 1987). Intravenous absorption of irrigating fluid starts only when the intravesical pressure has reached the pressure in the prostatic veins, but it will then take a relatively long time to fill the bladder due to irrigating fluid leakage into the circulation.

The finding in the present study, that the pressure gradient necessary to induce EVA exists much earlier during the filling phase of the bladder, supports the conclusion of Hahn *et al.* (1987). Thus the critical intravesical pressure when irrigating fluid enters the perivesical space is lower than when it enters the circulating blood. There might also be a "punctured balloon" effect with EVA, but this situation is more complex than IVA, since there may be some blocking of the capsular perforations in addition to accumulation of the leaking fluid around "the balloon".

The significance of this study for the surgeon performing TURP is that the valid pressure gradient for extravascular absorption is equivalent to the transmural bladder pressure. This exists very early in the filling phase and should be taken into account when open perforations of the prostatic capsule are created. It may under certain circumstances induce large extravascular absorptions, even when the intravesical pressure is below that in the prostatic veins.

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Three-monthly GnRH Agonist (Buserelin) for Prostatic Cancer

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Summary—A new slow release formulation of buserelin given as a 3-monthly depot injection has been evaluated in 4 patients with advanced prostatic cancer previously maintained on shorter acting depots. Treatment was maintained for a mean period of 21 months. Steady state urinary buserelin concentrations were reached by the beginning of the third treatment week and maintained until the end of the third treatment month. Serum testosterone remained suppressed in the castrate range for the duration of the study. Seven previously untreated patients were entered into treatment. Serum testosterone was suppressed into the castrate range between the seventh and fourteenth days after implantation. This preparation offers an advantage for the patient and clinician over existing methods of GnRH analogue administration and will now enter further clinical trial.

Gonadotrophin releasing hormone agonists were initially used as 5 or 6 times daily nasal spray insufflations (Waxman *et al.*, 1983) or once daily subcutaneous injections (Allen *et al.*, 1983). These compounds provide an effective and safe alternative to orchiectomy and are without the cardiovascular toxicities of oestrogen therapy (Garnick, 1986). In order to improve treatment, depot preparations effective in suppressing testosterone if given once monthly were synthesised (Williams *et al.*, 1984; Waxman *et al.*, 1986). Recently, longer acting peptide delivery systems have been developed, effective in suppressing testosterone if administered once every 2 months (Waxman *et al.*, 1989). These peptide delivery systems have been further improved and recently a new preparation effective in non-human primates in suppressing gonadal steroid production for more than 3 months has been manufactured (Fraser *et al.*, 1987). We have performed a pharmacological and endocrine evaluation of this new 3-month depot preparation in men with prostatic cancer.

Patients and Methods

Four patients were studied who had previously been treated for a mean period of 1.8 years (range 1–2.4) with depot D-Ser $(TBU)^6$-LHRH ethylamide (buserelin) given at an initial dosage of 3.3 mg once monthly and then 6.6 mg 2-monthly. All patients had had a complete response to treatment which was maintained at the start of the study. Each 3-month depot implant consisted of a 1 cm long core of lactide-glycolide co-polymer containing 10 mg buserelin. Treatment was given by injection into the subcutaneous tissue of the anterior abdominal wall through a 14 gauge needle and continued for a mean period of 21 months (range 21–24). During this period urinary buserelin excretion was measured at weekly intervals. Following the initial pharmacokinetic results obtained in these patients, 7 previously untreated patients were entered into the study. Each patient received cyproterone acetate 100 mg *p.o.* thrice daily for 1 week before treatment and the first 4 weeks of 3-monthly depot buserelin treatment. This is because this regimen has been shown to abrogate tumour flare in patients with prostatic cancer treated with gonadotrophin releasing hormone analogues (Waxman *et al.*, 1988). In these previously untreated patients serum testos-

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Based on a Poster Demonstration at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

terone was measured prior to treatment, then weekly for 1 month and monthly thereafter. Urinary buserelin levels were measured weekly. Testosterone was assayed using a standard single antibody radioimmunoassay (significant assay cross-reactivity was with 5 alpha dihydrotestosterone 8%, 19 nortestosterone 47% and androstenedione 3%; assay sensitivity was 0.1 nmol/l, intra-assay precision 5–8%, inter-assay precision 6–8%). Buserelin was measured by double antibody radioimmunoassay (no cross-reactivity with GnRH or GnRH peptide fragments, assay sensitivity 10 pg per tube, intra-assay precision 11% and inter-assay precision 17%; 1 ng/ml = 0.81 nmol/l) (Sandow and Clayton, 1981).

Results

Urinary buserelin levels are shown in Figure 1 and described in the Table. Figure 2 details serum testosterone levels in the 4 patients treated for up to 2 years. Serum testosterone concentrations were maintained at very low levels for the duration of therapy. In the previously untreated patients, mean serum testosterone before treatment was 8.7 nmol/l (range 5.4–12.1), decreasing after 7 days' treatment with cyproterone acetate to a mean concentration of 2.5 nmol/l (range 0.5–4.0) on the day of implantation. Seven days after implantation the serum testosterone concentration was 2.4 nmol/l (range 0.4–5.8), remaining in the castrate range (<2.5 nmol/l) for all patients for the remainder of treatment.

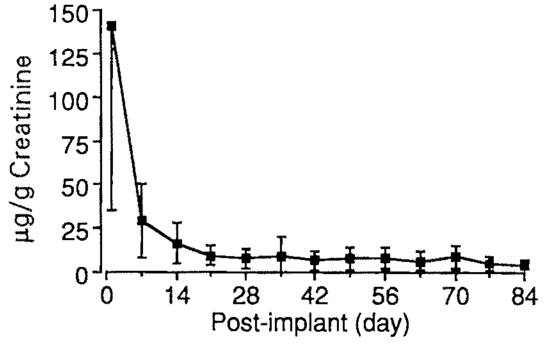
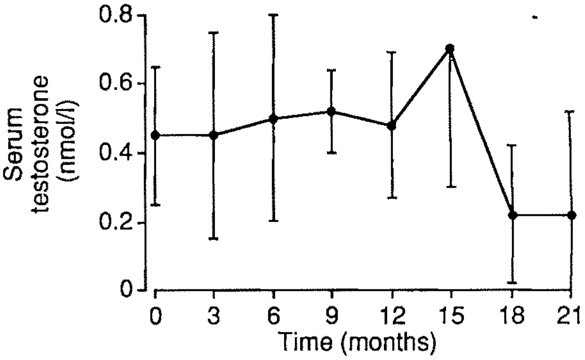


Fig. 1 Buserelin excretion.

Table Urinary Buserelin Excretion

Post-implant day	*Buserelin concentration mean (standard error)*	*Observations (n)*
1	141.2 (106.4)	15
7	29.6 (21.2)	15
14	16.6 (11.4)	16
21	9.5 (5.9)	14
28	7.6 (5.1)	16
35	8.7 (11.6)	16
42	6.8 (5.4)	16
49	7.6 (6.4)	16
56	8.1 (6.1)	16
63	6.4 (5.2)	16
70	8.6 (6.7)	16
77	5.3 (4.1)	16
84	4.4 (2.8)	15

(Summated results of 4 treatment cycles in 4 patients).



Normal range 12-38nmol/l
Castrate range <2.5nmol/l

Fig. 2 Serum testosterone levels.

Discussion

This pharmacokinetic study has shown the sustained, controlled release of buserelin to be effective in achieving and maintaining castrate levels of testosterone. In the 4 patients pre-treated with earlier shorter acting formulation of buserelin, the 3-month depot was introduced in a trial situation in order to investigate its efficacy. The release characteristics of the preparation were such as to maintain serum testosterone in the castrate range for periods of up to 2 years. Having demonstrated the activity of this compound, previously untreated patients were entered into the study. The 3-month formulation in these 7 patients achieved rapid suppression of serum testosterone into the castrate range within 1 week of implantation. The use of this new 3-month depot preparation has obvious advantages over shorter acting formulations. Further clinical evaluation of this new preparation is proceeding.

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Significance of Histological Prognostic Indicators in Patients with Carcinoma of the Prostate

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Summary—The relationships between histological prognostic indicators and their relative significance in prognosis were studied in 139 patients who underwent radical prostatectomy. The estimated progression rates at 5 and 8 years were 14 and 52% respectively for patients with high grade tumours, 25 and 50% for those with capsular penetration, 31 and 58% for patients with seminal vesicle invasion and 23 and 55% for those with lymph node metastases. Each of the 4 parameters yielded an approximately equal increased risk of disease progression at 5 and 8 years. The occurrence of 2 or more risk factors in the same patient did not result in a statistically increased risk of progression at 5 and 8 years. The effect of capsular involvement on progression was directly related to the extent of invasion. The progression rate at 8 years was 3% for patients with mild involvement, 19% for those with extensive invasion and 50% for those with capsular penetration.

The prognosis of patients with carcinoma of the prostate who undergo radical prostatectomy is affected by tumour grade and surgical (pathological) stage (Brown *et al.*, 1982; Catalona *et al.*, 1982; Elder *et al.*, 1982; Middleton *et al.*, 1986; Paulson *et al.*, 1986; Mukamel *et al.*, 1987). The best results for radical prostatectomy are reported in patients with tumours confined to the prostate (Walsh and Jewett, 1980; Elder *et al.*, 1982; Middleton and Smith, 1982; Paulson *et al.*, 1982; 1986). Patients with high grade tumours or extraprostatic tumour extension have a higher incidence of treatment failure than those with low grade tumours or tumours confined to the prostate. Histological findings of a high tumour grade, capsular invasion, seminal vesical invasion and lymph node metastases each indicate an unfavourable prognosis (Brown *et al.*, 1982; Catalona *et al.*, 1982; Elder *et al.*, 1982; Middleton *et al.*, 1986; Paulson *et al.*, 1986; Mukamel *et al.*, 1987). Various combinations of these findings are frequently found on microscopic examination, but their relative significance in determining prognosis remains unclear.

The present study was undertaken to determine the relationships between the various prognostic indicators in a large group of patients who underwent radical prostatectomy and to determine their relative significance in affecting disease progression, local recurrence and survival.

Patients and Methods

The study group comprised 139 patients, aged 42 to 76 years, with carcinoma of the prostate who underwent radical prostatectomy between 1975 and 1985. They were selected from the total radical prostatectomy population according to the availability of follow-up data. Radical prostatectomy was performed in patients with tumours which were clinically confined to the prostate (clinical stages A2, B1, B2), with a normal serum acid phosphatase and a negative skeletal survey. Those with clinical evidence of local tumour extension were referred for irradiation therapy. In this group, 119 patients underwent retropubic prostatectomy with lymph node dissection and 20 underwent perineal prostatectomy without lymph node dissection. Following surgery, the areas thought to be cancerous were outlined on every specimen and histological map-

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ping was performed. Each prostate was cut serially and sections from the proximal urethra, the apex of the prostate and distal urethra, the seminal vesicles and the prostate capsule were examined for histological staging; 20 to 30 blocks from each specimen were examined. Capsular involvement was graded from 1 to 3 according to the level of invasion, as suggested by McNeal *et al.* (1986). Level 1 indicated mild capsular involvement in the area adjacent to the prostatic cancer. Level 2 indicated extensive invasion with involvement of most or the whole width of the prostatic capsule but without penetration through the capsule. Level 3 implied involvement of the whole width of the capsule with penetration of the tumour to periprostatic tissues. Tumour grading was carried out according to the M. D. Anderson grading system (Brown *et al.*, 1982).

Clinical data were obtained from the patients hospital charts and from the UCLA Medical Center Registry records. From the collected data, the incidence of each of the histological prognostic indicators, as well as the relative significance of these findings in affecting disease progression, was determined. Progression was defined as biopsy-proven local recurrence as the first evidence of progression and/or appearance of skeletal metastases by plain radiographs and/or bone scan. Persistently elevated acid phosphatase was also regarded as progression.

Time to progression, local recurrence and metastases were estimated by the method of Kaplan and Meier. Comparison between the different groups of patients was made by means of the Mantel Cox log rank test or the chi-squared test. Multivariant assessment of variables was made with the Cox Proportional Hazards Model.

Results

The relationships between disease progression, tumour grade, the extent of capsular involvement, seminal vesicle invasion and lymph node metastases are presented in Tables 1 to 4.

The estimated disease progression rate at 8 years was zero for grade 1, 19.1% for grade 2, 30.7% for grade 3 and 40.1% for grade 4 tumours (Table 1, Fig. 1A). The extent of capsular invasion, correlated with disease progression rates at 8 years, showed a progression rate of 30% for patients with mild capsular involvement (level 1), 19% for those with extensive involvement (level 2) and 50% for those with capsular penetration (level 3) (Table 2, Fig. 1B). When the seminal vesicles were not involved, the disease progression rate at 8 years was 16% compared with 58% for patients with seminal vesicle involvement (Table 3, Fig. 1C). Disease progression was found in 17% of patients with no lymph node metastases and 55% of those with lymph node metastases (Table 4, Fig. 1D).

Table 1 Estimated 5- and 8-year Rates for Time to Progression as Related to Tumour Grade

		% Progression	
*Tumour grade**	*No. progressed/total*	*5 years*	*8 years*
1	0/29	0	0
2	3/35	5.6	19.1
3	6/31	8.8	30.7
4	8/44	17.9	40.1

* M. D. Anderson classification.

Table 2 Estimated 5- and 8- year Rates for Time to Progression as Related to Capsular Involvement

		% Progression	
Capsular involvement	*No. progressed/total*	*5 years*	*8 years*
Mild (Level 1)	2/38	3	3
Extensive (Level 2)	4/53	2	19
Capsular invasion (Level 3)	11/48	25	50

Table 3 Estimated 5- and 8-year Rates for Time to Progression Related to Seminal Vesicle Involvement

		% Progression	
Seminal vesicles	*No. progressed/total*	*5 years*	*8 years*
Not involved	7/104	3	16
Involved	10/35	31	58

Table 4 Estimated 5- and 8-year Rates for Time to Progression Related to Node Metastases

		% Progression	
Lymph nodes	*No. progressed/total*	*5 years*	*8 years*
Not involved	9/27	5	17
Involved		23	55

The relationships between unfavourable prognostic indicators, *i.e.* high grade tumours, capsular penetration, seminal vesicle invasion and lymph node metastases, are presented in Table 5. Of patients with grade 3 and 4 tumours, 53.9% also

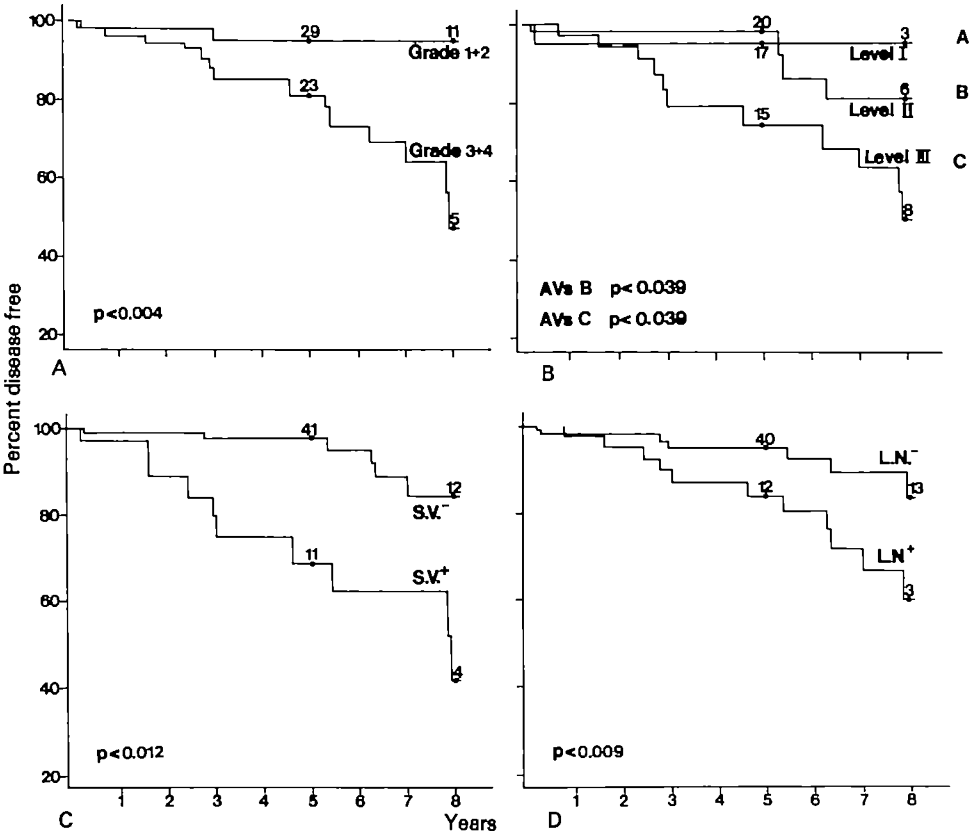

Fig. 1 (A) Time to progression Kaplan Meier curves for tumour grade. (B) Capsular involvement. (C) Seminal vesicle (S.V.) invasion. (D) Lymph node (L.N.) metastases. The numbers indicate the number of patients remaining at risk at 5 and 8 years. The P value is the Mantel Cox log rank comparison of the Kaplan Meier curves.

had capsular invasion, 42.1% had seminal vesicle invasion and 27.1% had lymph node metastases. Of those with capsular invasion, 85.4% had high grade tumours, 52.1% had seminal vesicle invasion and 37.5% had lymph node metastases. Of patients with seminal vesicle invasion, 88.4% had high grade tumours, 75% also had capsular penetration and 47.2% had lymph node metastases; 75% of patients with lymph node metastases had high grade tumours, 60.7% had capsular invasion and 60.7% had seminal vesicle invasion. Statistical analysis (using the Cox Proportional Hazards Model) of these data showed that the occurrence of 2 or more risk factors in the same patient did not place him at a statistically increased risk of progression at 5 and 8 years.

Table 5 Relationship Between Unfavourable Prognostic Indicators: High Grade Tumours, Capsular and Seminal Vesicle Involvement and Lymph Node Metastases

		No. (%) of patients with			
Histological findings	*No. of Patients*	*Grade 3, 4 tumours*	*Capsular invasion*	*Seminal vesicle invasion*	*Lymph node metastases*
Grade 3, 4 tumours	76	—	41 (53.9)	32 (42.1)	21 (27.1)
Capsular penetration	48	41 (85.4)	—	25 (52.1)	18 (37.5)
Seminal vesicle invasion	36	18 (88.4)	27 (75.0)	—	17 (47.2)
Lymph node metastases	28	21 (75.0)	17 (60.7)	17 (60.7)	—

Local recurrence as first evidence of progression, and metastatic rates at 8 years, as related to capsular invasion are presented in Table 6. No local recurrence or distant metastases were found in patients with mild (level 1) capsular involvement, whereas 2% of those with extensive (level 2) capsular involvement had local recurrence and 18% had distant metastases. When capsular penetration (level 3) was noted, the local recurrence rate was 17% and the metastatic rate 37%.

The analysis of patient survival showed the same pattern as time to progression. However, with only 5 deaths to date, valid statistical analysis cannot be performed. It should be noted that all 5 patients who died had high grade tumours as well as capsular penetration. Four of these patients also had seminal vesicle invasion.

Discussion

The increased incidence of lymph node metastases in patients with carcinoma of the prostate has been reported in those with high grade tumours, tumour extension beyond the capsule and seminal vesicle invasion (Flocks *et al.*, 1959; McNeal, 1969; Grossman *et al.*, 1980; Paulson, 1980; Stamey, 1982). Kramer *et al.* (1980) showed that lymph node metastases indicated a potential for systemic spread and that the majority of patients developed distant metastases within 5 years regardless of therapy. The significance of seminal vesicle invasion in affecting prognosis was demonstrated in reports from the Johns Hopkins Hospital (Walsh and Jewett, 1980; Elder *et al.*, 1982). Of the 17 patients who underwent radical prostatectomy and who had seminal vesicle invasion, none survived for 15 years and 60% had recurrent cancer. These findings were confirmed in a recent study from our institution (Mukamel *et al.*, 1987) showing a local recurrence rate of 23.6% at 8 years in patients with seminal vesicle invasion and a 24.4% incidence of distant metastases. Paulson *et al.* (1986) reported, in a group of 143 patients who underwent radical prostatectomy, a treatment failure rate of 8% in patients with tumours confined to the prostate and 14% in those with tumour extension beyond the capsular margin. Extension of tumour to seminal vesicles was the most significant predictor of subsequent recurrence, and the probability of treatment failure was related to the Gleason sum of the primary tumour.

Table 6 Local Recurrence Rates and Metastastic Rates at 8 Years Related to Capsular Invasion

Capsular invasion	*Local recurrence rate (%)*	*Metastatic rate (%)*
Mild (Level 1)	0	0
Extensive (Level 2)	2	18
Penetration (Level 3)	17	37

In the present study, the relative significance of high tumour grade, capsular invasion, seminal vesicle invasion and lymph node metastases in affecting prognosis was investigated. Each of the 4 prognostic indicators was found to yield an approximately equal increased risk of disease progression. The occurrence of 2 or more risk factors in the same patient did not place him at a statistically increased risk of progression. These findings are explained by the close inter-relationship between the 4 factors. The presence of each of the 4 histological findings is related to the presence of the other 3, as shown in Table 5. It is of interest that the significance of nodal metastases in altering prognosis was not greater than that of the other 3 findings. This is explained by the inclusion in the study of patients with only minimal lymph node involvement. Those with extensive lymph node involvement diagnosed during lymph node dissection were not treated with radical prostatectomy and were not included in the study.

Although capsular invasion is considered to be an ominous prognostic indicator, the significance of the extent of invasion was not well documented in previous reports. Middleton *et al.* (1986) showed that the prognosis of patients with capsular invasion was similar to that of patients with tumours confined to the prostate. In that study, capsular invasion was defined as microscopic invasion of the capsule, although the extent of invasion was not mentioned; 12 of 14 patients with tumour extension into the capsule were free of disease 5 years after radical prostatectomy, compared with 5 of 10 patients with seminal vesicle invasion.

McNeal *et al.* (1986) examined the patterns of progression in prostate cancer. Their study included 100 prostates removed at necropsy and 38 removed by radical prostatectomy. It was found that tumour volume, histological differentiation, capsular invasion, seminal vesicle invasion and metastases were highly inter-related. In both the necropsy and the radical prostatectomy series, penetration of the capsule by the tumour was significantly related to metastases. The data presented in our series, which included only patients who underwent radical prostatectomy, support the findings of McNeal *et al.* (1986) and provide further information on disease progression related to different levels of capsular involvement. We have shown that disease progression rates at 8 years were directly related to the extent of invasion: 3% for mild involvement, 19% for extensive involvement and 50% for capsular penetration. Both local recurrence rates and metastatic rates were related to the extent of capsular invasion. Mild involvement had no effect on disease progression, but more extensive involvement produced local recurrence rates and metastatic rates at 8 years of 2 and 18% respectively. A significant increase in both local recurrence and metastases rates, to 17 and 37% respectively, was noted when the prostatic capsule was penetrated by the tumour.

The results of this study indicate that all histological prognostic indicators are inter-related and the high risk factors are of similar significance in affecting prognosis. The extent of capsular involvement, as a valuable prognostic indicator, points to the importance of routine histological grading of capsular invasion.

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Complete Urethral Stricture of the Membranous Urethra: a Different Perspective

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Summary—Seven patients with complete rupture of the membranous urethra secondary to trauma were treated by internal optical urethrotomy (OU). All underwent initial suprapubic catheter drainage. The diagnosis of complete urethral rupture was confirmed by ascending and descending urethrograms and subsequent urethroscopy. OU was performed 3 weeks to 8 years following injury. Although all patients required further OUs for recurrent strictures, all can pass urine satisfactorily. Two patients have slight stress incontinence. This technique is a viable alternative to more conventional procedures for this condition.

Although complete rupture of the membranous urethra is an uncommon injury, its management and treatment remain one of the most controversial areas in urology. When compared with delayed urethroplasty, immediate exploration and realignment have not shown significantly different results (Jackson and Williams, 1974).

Most complete urethral ruptures are associated with pelvic fractures, usually resulting from road traffic accidents, and many patients have associated severe abdominal injuries. The function of the external sphincter is usually destroyed at the initial injury (Waterhouse *et al.*, 1980).

Continence then depends on the internal sphincter, which is a reliable structure in the male; subsequent injury to this sphincter by surgery or a misguided prostatectomy may result in incontinence. However, Morehouse and Mackinnon (1980), in their series of 58 complete ruptures treated by the delayed 2-stage Johanson (1953) technique, reported a remarkably low incidence of complications. Only 1 patient had mild stress incontinence and 5 remained continent following transurethral resection of the prostate; 90% of evaluable patients remained potent. They attributed this favourable outcome of the performance of initial suprapubic cystostomy at the time of injury followed by late repair.

Patients and Methods

All patients had an intravenous urogram at the time of injury; ascending urethrograms were not always performed then but were carried out prior to initial urethroscopy. None of the patients had rupture of the bladder or damage to the rectum and none had intra-abdominal injuries requiring laparotomy. All were treated by initial suprapubic catheter drainage. The diagnosis of complete urethral rupture was confirmed by ascending and descending urethrograms and subsequent urethroscopy.

Case Reports

G.F., aged 7 years, sustained a complete rupture of the membranous urethra by falling astride a bar in July 1985. Urethroscopy was performed 3 months later and initial internal optical urethrotomy was unsuccessful. Subsequently he required a further OU for partial recurrent strictures 6, 7, 9, 10, 11, 13 and 15 months following injury. He now has good flow and control; potency not assessable.

J.McD, aged 9 years, fell from a tractor, sustaining a complete rupture of his membranous urethra in October 1984. Urethroscopy and OU were performed 3 months after injury and again 2 weeks later for slight narrowing of the urethra at the site of injury. There was no recurrent stricturing following this procedure. He now has good flow and control; potency not assessable.

M.G., aged 24 years, sustained a crush injury which

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caused a pelvic fracture and complete rupture of his membranous urethra in August 1986. OU was performed 3 weeks later. Further OUs were performed for partial stricture at 5, 9 and 14 months and granulation tissue at the site of injury was resected at 12, 13, 15, 16, 17 and 19 months. This was a particularly difficult long complete stricture which required more frequent and prolonged treatment than the average case. He now has good flow and control but remains impotent.

M.M., aged 27 years, sustained a complete rupture of the membranous urethra in April 1974 and was treated with immediate suprapubic catheter drainage. An open repair 6 months later failed and the patient declined further surgery. Eight years later he developed problems with the suprapubic catheter and bladder stones and at this stage urethroscopy and OU were performed. He required further OU for partial stricture 2, 3, 5, 6, 7 and 8 months later, and also resection of granulation tissue at 9 and 11 months. Despite having a stroke in the spring of 1985, he has good flow with slight stress incontinence and remains impotent.

A.D., aged 35 years, had a pelvic fracture with complete rupture of the membranous urethra in March 1987. OU was performed 3 months from injury and again at 11 months. He now has good flow, slight incontinence, and remains impotent.

M.S., aged 25 years, had a pelvic fracture with complete rupture of his membranous urethra in February 1987. Urethroscopy and OU were performed 3 months after injury and on 3 other occasions for recurrent partial stricture. He now has good flow and control but remains impotent.

T.McA., aged 54 years, sustained a pelvic fracture with complete rupture of his membranous urethra in August 1986. Urethroscopy and OU were performed 9 months after injury and 6 and 10 weeks later for recurrent strictures. He now has good flow and control but remains impotent.

Operative Technique

Cystoscopy is performed through the suprapubic track, which may require dilatation to accept the instrument. The bladder neck is inspected and it is usually possible to pass the cystoscope into the prostatic urethra as far as the verumontanum. An optical urethrotome is passed through the urethra as far as the stricture in the membranous part. The stricture is invariably complete in these cases. Looking through the suprapubic instrument, movement of the stricture with manipulation of the urethrotome in the membranous urethra can be seen. This, in conjunction with a recent antegrade and retrograde urethrogram, provides an indication of the position of the blind end of the urethra. A sound placed in the prostatic urethra from above can also be of assistance.

It must be remembered that there is invariably posterior displacement of the prostatic urethra compared with the membranous part. This is what Mitchell (1968) referred to as the "S bend". Urethrotomy is performed cutting in a backward direction towards the veru. Occasionally, when near the proximal urethra, if the light to the suprapubic cystoscope is turned off, light from the urethrotome can be seen as a glow through the tissues. Eventually the blade of the urethrotome can be seen from the bladder, emerging through the stricture into the prostatic urethra in the region of the external sphincter. At this stage the cystoscope is removed from the bladder and replaced by a Heygrove's dilator which is guided under direct vision via the urethrotome through the urethra to emerge at the external urethral meatus. An 18F Silastic Foley catheter is tied to the dilator and pulled into the bladder. A 20F suprapubic catheter is left through the suprapubic track.

The procedure is facilitated if 2 surgeons can work simultaneously from above and below, but it can also be performed by a single operator.

The optimal duration of urethral catheterisation following urethrotomy is unknown (Mitchell, 1968). It is wise to leave the suprapubic catheter *in situ* until the urethra has stabilised. Our current practice is to remove the urethral catheter at 3 weeks and allow the patient to pass urine. Further urethrotomies or urethral dilatations are undertaken as indicated clinically.

Results

Urethrotomy was performed 3 weeks to 8 years after injury. In all cases it was possible to establish communication between the bulbar and prostatic urethra. Following removal of the urethral catheter all patients voided satisfactorily. All developed recurrent partial strictures which required further urethrotomies or resection of granulation tissue (mean 7, range 2–10). Two patients (J.McD. and A.D.) required only 1 further urethrotomy following the initial procedure at 2 weeks and 11 months respectively. Three patients (T.McA., M.S. and M.G.) required between 2 and 3 further OUs at varying intervals from 1 to 5 months. The remaining 2 patients (G.F. and M.M.) required more frequent urethrotomy at monthly intervals on 7 and 6 occasions respectively. M.M. also required resection of granulation tissue at the site of the stricture 9 and 11 months from injury. Resection of granulation tissue was also required in M.G. on 6 occasions. Eventually, however, the urethra stabilised in all patients and all can void satisfactorily. Five have perfect control and 2 have slight stress incontinence.

All urethrotomies were covered with single dose intravenous antibiotics (netilmicin or methicillin) and there were no episodes of bacteraemia. Bleeding requiring transfusion was a problem in 1 patient (M.G.) following deep resection of granulation tissue at the site of the stricture; however, this stopped spontaneously and required no further treatment.

Discussion

There are 2 main controversies regarding complete rupture of the membranous urethra: the timing of the urethral repair and the best operative procedure to effect the repair.

Opinions differ on the optimal time for stricture repair. Turner-Warwick (1973) reported good results with immediate exploration and primary urethral repair, as did Blandy (1975), Glass *et al.* (1978) and Patterson *et al.* (1983). However, equally good results are achieved by immediate suprapubic drainage and late urethroplasty (Gardiner *et al.*, 1978; Webster *et al.*, 1983; Morehouse, 1988). Webster *et al.* (1983) analysed the outcome in 301 cases of complete rupture of the membranous urethra in 15 series, treated by immediate simple realignment over a splinting catheter. They found that recurrent strictures occurred in 69% of patients, impotence in 44% and incontinence in 20%. They felt that these result were poor when compared with those achieved using initial suprapubic drainage and delayed urethroplasty, as popularised by Johanson (1953), which appear to decrease the incidence of impotence and incontinence. Morehouse *et al.* (1972), Coffield and Weems (1977) and Sharlip (1981) take the view that primary realignment of the ruptured urethra increases the incidence of impotence and incontinence.

On the other hand, Patterson *et al.* (1983) advocated immediate realignment, believing that impotence after pelvic fracture and posterior urethral disruption is due to neurovascular injury secondary to the violent forces necessary to cause these injuries, and not due to subsequent surgery.

It is probably safe to say that the best form of treatment which will yield the fewest complications in the way of recurrent stricture, incontinence and impotence remains open to question (Jackson and Williams, 1974). Satisfactory results have been obtained with immediate open realignment and primary repair (Turner-Warwick, 1973; Blandy, 1975; Glass *et al.*, 1978); Waterhouse *et al.*, 1980; Patterson *et al.*, 1983), delayed scrotal skin substitution urethroplasty (Gardiner *et al.*, 1978; Webster *et al.*, 1983) and, more recently, delayed urethroplasty using pedicled preputial or penile skin (Mundy and Stephenson, 1988).

There is no doubt that excellent results can be obtained by those who have developed a special interest and expertise in this field. Complete rupture of the membranous urethra is an uncommon injury and the average urologist, who is unlikely to see more than 5 cases per year, cannot expect to achieve such good results. Many of these patients present initially to a hospital where urological expertise is unavailable. Associated injuries make transfer inappropriate and the initial treatment is necessarily undertaken by a general surgeon. In this situation, immediate suprapubic catheterisation and delayed treatment of the stricture have obvious advantages.

Delayed optical urethrotomy for complete rupture of the membranous urethra using transvesical endoscopy of the proximal urethra has been described by Gonzalez *et al.* (1983). Lewis and McCullough (1985) described a flexible fiberoptic nephroscope for the evaluation of complete urethral strictures prior to repair with open urethroplasty. Towler and Eisen (1987) have successfully used a technique similar to our own in the treatment of 5 patients with incomplete strictures. At that time they had not had the opportunity to apply the technique to a complete urethral stricture.

Opinions vary as to the optimal time to perform urethroscopy following urethral trauma. Immediate examination is unlikely to provide more information than a urethrogram and may cause further damage to the urethra. Between 3 and 6 weeks from injury allows time for the suprapubic track to mature and the periurethral haematoma to reduce in extent, without allowing time for significant fibrosis to develop. However, urethrotomy can be performed at any late stage and was carried out successfully in a patient 8 years after injury. Internal optical urethrotomy causes the patient less trauma during both initial treatment and late management of the stricture; patient acceptance is high and the incidence of impotence may be reduced. All of our patients are impotent, although 3 are still too young to evaluate potency. This may be due to the severe nature of their pelvic injuries, as evidenced by the strictures, which were all complete with significant separation of the ends of the urethra (Fig.). The technique of optical urethrotomy is most suited to short strictures, but it is possible to use it for

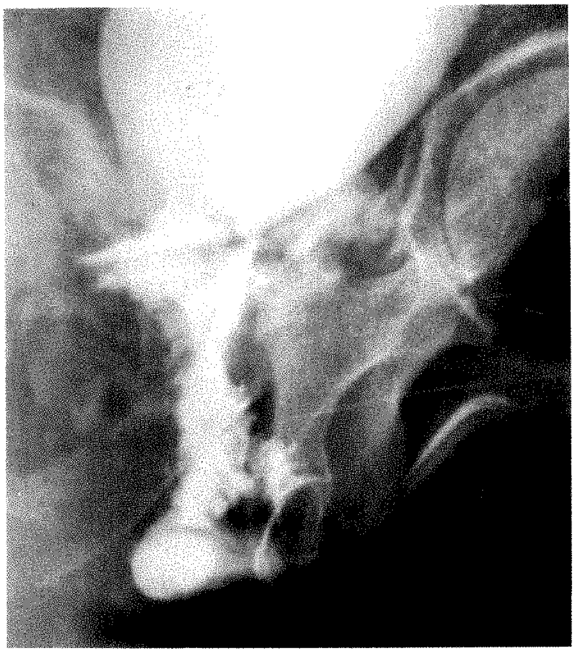

Fig. Typical separation of urethral ends with extravasation of contrast on ascending urethrogram and intravenous urogram at time of injury.

strictures extending over 2 cm. It is suitable for all ages and does not prevent the subsequent performance of an open urethroplasty if necessary.

The technique of optical urethrotomy for complete strictures is not particularly easy, but should present no undue difficulty for those with sufficient experience of OU. Appreciation of the posterior displacement of the prostatic urethra in relation to the membranous urethra is important in order to prevent the creation of an anterior false passage to the bladder. Simultaneous urethroscopy and suprapubic cystoscopy with the cystoscopy in the prostatic urethra is particularly helpful in achieving correct realignment.

We believe that delayed optical urethrotomy is a viable alternative to open urethroplasty in patients with complete rupture of the membranous urethra.

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Comparison of Catheter Surface Morphologies

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Summary—The surface morphologies of different generic types of Foley catheter have been investigated using scanning electron microscopy (SEM). The characteristic features of each material are illustrated and it is shown that distinct differences exist between the inner and outer surfaces of latex-based catheters; these differences are attributed to the methods of manufacture. The possible relations between morphology and performance *in situ* are discussed.

A wide choice of Foley catheters, made by a number of manufacturers, is now available. Various attributes, such as biological inertness, ease of insertion and resistance to encrustation are claimed for these different brands. There remains, however, a lack of awareness of how the construction of the various types of catheter determines their surface morphology, and how this might influence performance *in vivo*.

Foley catheters are usually constructed from either pure silicone or latex, although polyvinyl chloride (PVC) catheters are also to be found. Those referred to as "all-silicone" or "100% silicone" are of wholly silicone construction, although a filler such as silica is generally employed to confer mechanical strength. They are often chosen for long-term use because silicone is considered to be particularly inert biologically; in addition, there is evidence that these catheters encrust less easily (Bruce *et al.*, 1974) and are less cytotoxic than some latex ones (Wilksh *et al.*, 1983; Talja *et al.*, 1986). Latex-based catheters are made from natural rubber latex and are usually coated to improve their surface properties. Although this material has been used for catheter construction for many years (Zorgniotti, 1973), it remains the material of choice because it combines mechanical strength and flexibility with relative inertness. The coatings applied to these catheters may either form separate layers overlying the surfaces or be applied to modify the latex surfaces themselves.

Latex catheters described as "siliconised", "silicone-treated" or sometimes "silicone-coated" have been impregnated with silicone oil. This is primarily to reduce friction and hence aid insertion into the urethra. The oil is believed to permeate out of the latex surface during the first few hours *in situ* (Talja *et al.*, 1986).

Another type of coating, applied as an external layer, contains polytetrafluoroethylene (PTFE), a substance known to be highly inert. This coating comprises a suspension of PTFE particles in a carrier polymer such as polyurethane and so is not a solid PTFE skin, as has been implied by Talja *et al.* (1986). Pure silicone elastomer may also be used as a coating, such catheters usually being unambiguously described as "silicone elastomer-coated". This layer must be well bonded to the underlying latex substrate if it is not to delaminate during use. The first examples of this type of catheter (Silastic) were introduced by Dow Corning; unfortunately this brand name is sometimes ambiguously used in the literature as a generic name for catheters of this type.

A more recent development is the latex catheter coated with a hydrogel. These polymers absorb water to become soft gels and are renowned for their biocompatibility (Ratner and Hoffman, 1976). Such coatings hydrate when in contact with the urethral mucosa, becoming slippery and making insertion easier; there is also evidence that they may resist encrustation (Eckstein *et al.*, 1984; Miller, 1975; Cox *et al.*, 1988).

Materials and Methods

Nineteen brands of Foley catheters were selected for examination (4 brands with coatings containing

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PTFE and 5 brands each of 100% silicone, siliconised latex and silicone elastomer-coated latex types). Four brands representing the 4 main types were thoroughly investigated, with samples being taken from more than 10 catheters in each category. Between 1 and 4 samples of the remaining brands were taken, single samples sufficing where the appearance appeared to conform closely to the type characteristics. Samples approximately 4 mm × 8 mm were cut from the catheters at a point immediately distal to the balloon (a region which is frequently found to have most encrusting deposits adhering to the lumen on used catheters).

No dehydrating or fixing procedures were carried out, since catheter materials (with the exception of those coated with a layer of hydrogel) are robust polymers containing little or no water within their structures; indeed any solvent treatment might damage them. Samples were mounted using either silver paint or Leit-C Plast (a conductive plasticine-like material). Particular attention was paid to ensuring generous electrical (and hence thermal) contact from the upper surface of the sample to the stub. Gold sputtering was carried out in an Edwards S150 sputterer at a current of 20 mA using specimen cooling. Because the samples are relatively thick insulators with poor electrical and thermal conductivity, special care was required to prevent overheating and so avoid the introduction of artefacts such as surface cracks. Micrographs in the published literature (Talja *et al.*, 1986; Axelsson *et al.*, 1977) show features which, on the basis of this work, would appear to be artefacts due to dehydrating, fixing or overheating. If, in spite of these precautions, surface cracks appear to be a consistent feature of the surface, this may be verified by examining an untreated catheter sample using scattered light, *e.g.* dark field or low angle illumination in a reflection microscope. Samples were examined in a Cambridge Stereoscan S360 at an accelerating voltage of 20 kV and a specimen tilt of 45°. Both inner and outer surfaces were examined. Micrographs with an original magnification of 500 times are presented here, as this best demonstrates the characteristic features of each material.

Three representative catheters from each of the 4 types described above are shown in the Figures.

Results

Figure 1 shows the outer and inner surfaces of 3 brands of all-silicone catheter. It can be seen that both surfaces appear very similar, being fairly smooth and also rippled, but with no obvious cracks. Occasional inclusions found in the surface may be attributed to particles of filler.

Siliconised latex catheters are shown in Figure 2. Since the surface is merely impregnated with silicone oil, the surface contours are in effect similar to those of the latex catheter, although the smoothness is determined by the treatments employed by the various manufacturers. A common feature is that the outer surfaces are rippled and fissured into "pavements" some 30 to 100 μm across, with variations in the microscopic texture. The inner surfaces, however, are quite different, being extremely rough and showing more variation between brands than is the case with the outer surfaces.

The surfaces of latex catheters with a coating containing PTFE are shown in Figure 3. Although the outer surfaces are smoother than those of siliconised latex, especially when viewed at higher magnifications, these too are rippled and fissured into roughly rectangular "pavements'. The inner surfaces are similarly very rough.

Figure 4 illustrates silicone elastomer-coated catheter surfaces. All brands investigated had extremely smooth outer surfaces, although debris was often present. The inner surfaces differed considerably from those in previous Figures, in that they were somewhat smoother.

Discussion

From these micrographs it is apparent that different types of catheter have very different surface topographies and that within each type different brands may also vary somewhat. Overall, the surface roughness is determined both by the materials used and the manufacturing methods employed.

The inner and outer surfaces of 100% silicone catheters are very similar because they are made by an extrusion process, producing the smooth rippled surfaces shown in Figure 1. However, the latex-based catheters shown in Figures 2 and 3 have inner and outer surfaces that differ considerably. Clearly the supposition of Talja *et al.* (1986), based on the earlier work of Dathe (1973), that the inner and outer surfaces are identical because the construction is wholly of latex is incorrect. This is because such catheters are made by repeatedly dipping a rod-shaped former into liquid latex until the desired thickness is achieved (coagulating the latex in between dips before finally curing it). The outer surface is therefore dried whilst exposed to air and has a surface morphology determined by factors such as curing temperature or the chemical

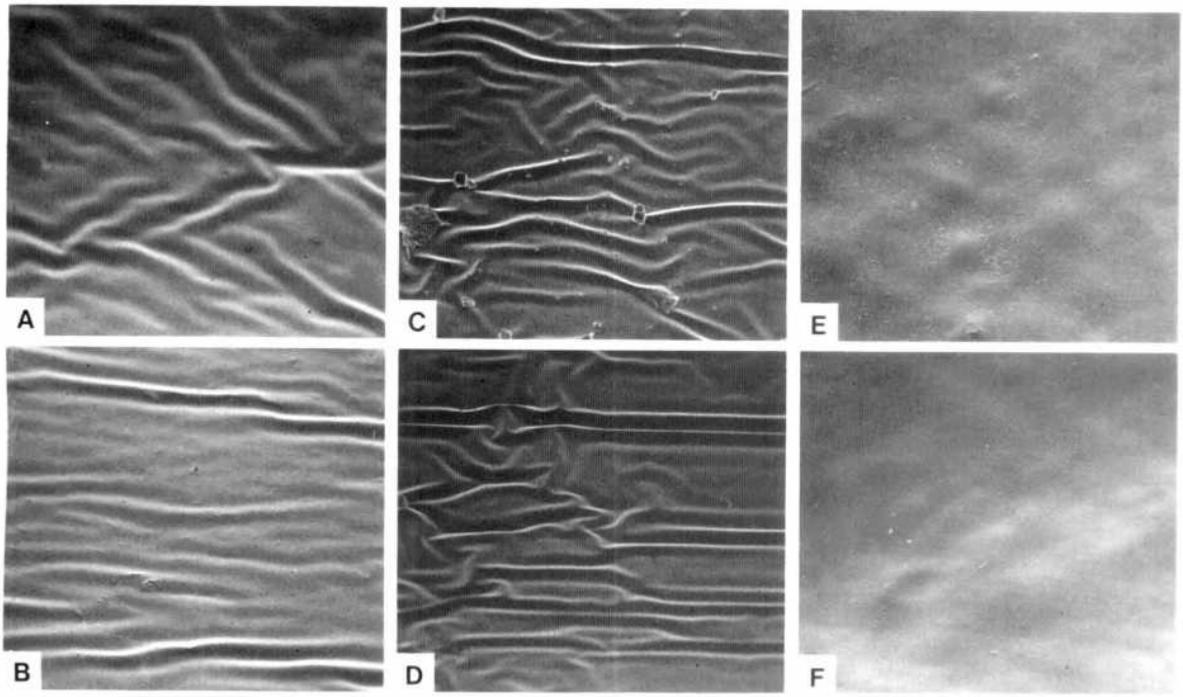

Fig. 1 Outer (A, C, E) and inner (B, D, F) surfaces of all-silicone Foley catheters (× 500). The catheter types shown are (A, B) Kendall Curity (The Kendal Co., Boston, USA), (C, D) Silicath (Travenol Laboratories S.A., Lessines, Belgium) and (E, F) Simpla (Simpla Plastics Ltd, Cardiff).

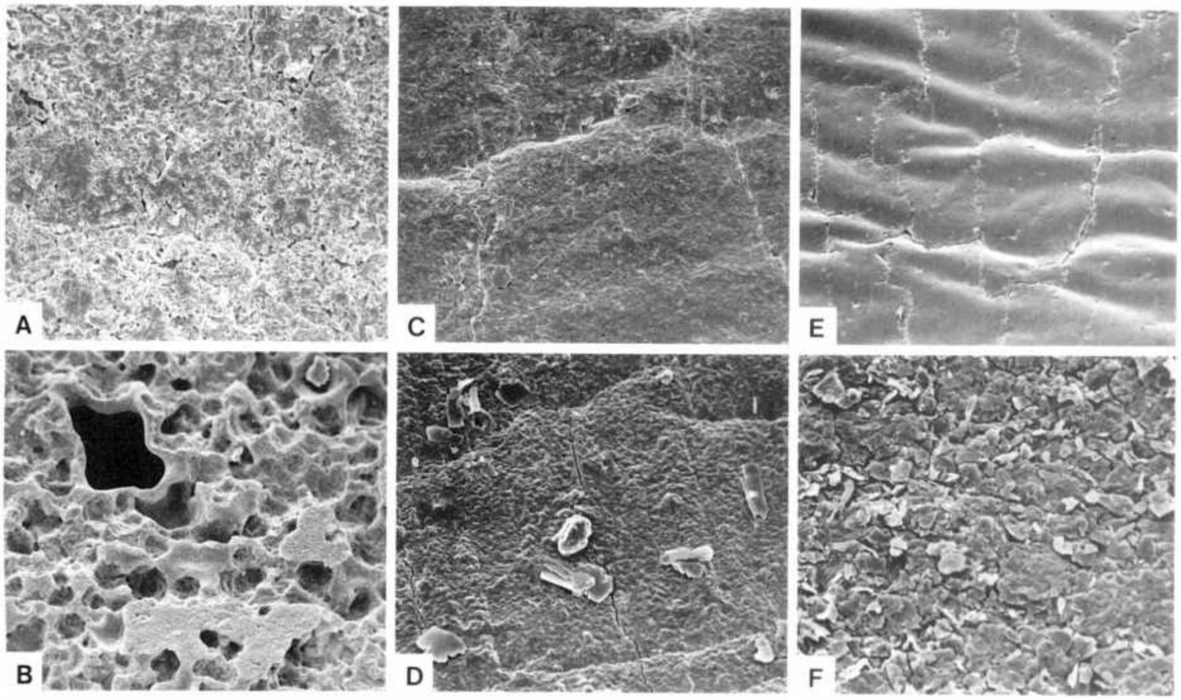

Fig. 2 Outer (A, C, E) and inner (B, D, F) surfaces of siliconised latex catheters (× 500). Catheters shown are (A, B) Kenguard (The Kendal Co., Boston, USA), (C, D) Rusch Gold Silkolatex (Willy Rusch A.G., Waiblingen, W. Germany) and (E, F) Porges, (Porges, Palaisean, France).

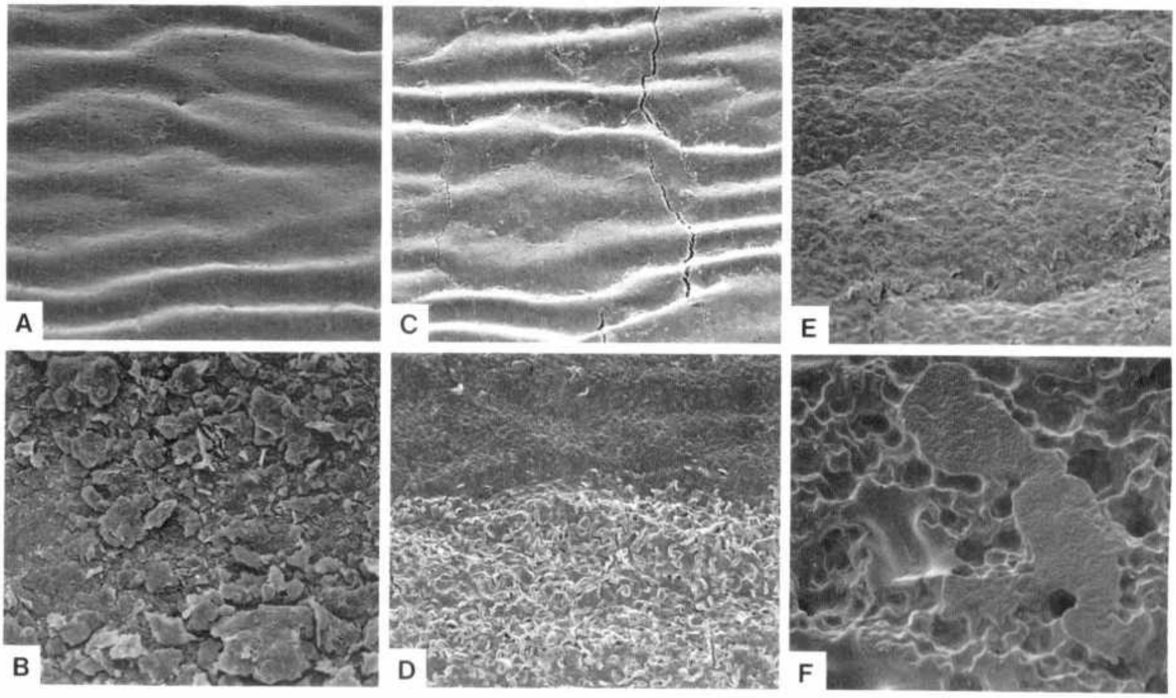

Fig. 3 Outer (A, C, E) and inner (B, D, F) surfaces of latex catheters with coatings containing PTFE (× 500). Illustrated are (A, B) Kendal Curity (The Kendall Co., Boston, USA), (C, D) Travenol (Travenol Laboratories Inc., Deerfield, USA) and (E, F) Warne (Warne Surgical Products Ltd, Lurgan, Co. Armagh).

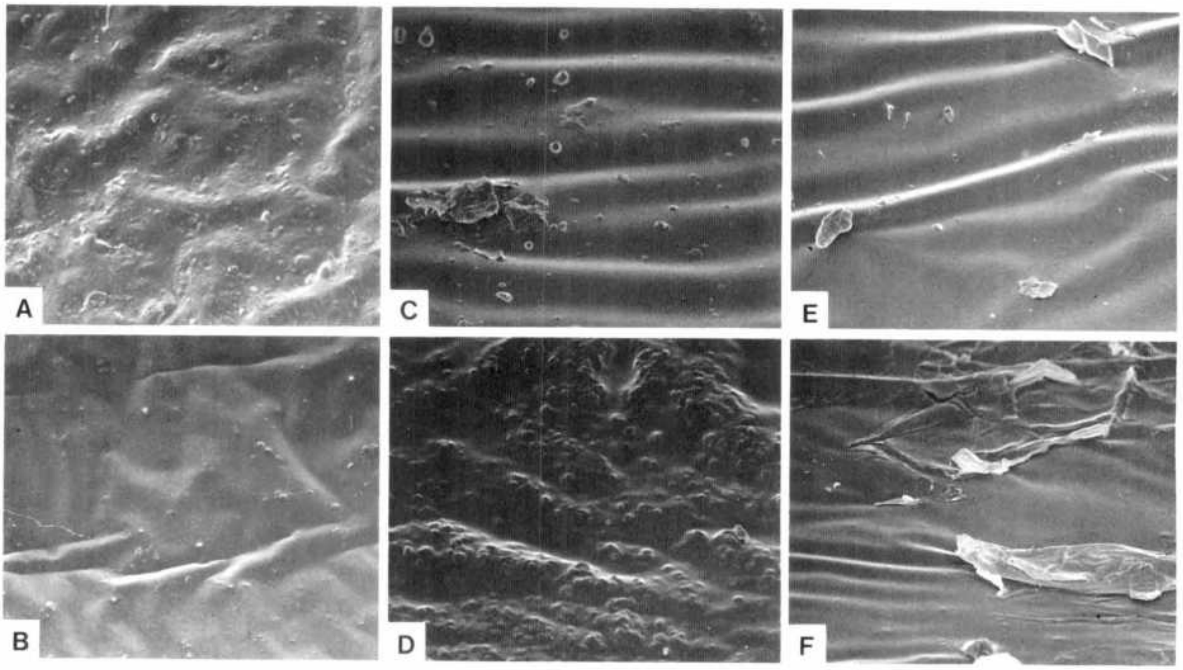

Fig. 4 Outer (A, C, E,) and inner (B, D, F) surfaces of silicone elastomer-coated latex catheters (× 500). (A, B) Bard (Bard Ltd, Clacton-on-Sea), (C, D) Accuseal (Squibb Surgical Ltd, Hounslow) and (E, F) Silastic (Dow Corning France S.A., Valbonne, France).

treatments used during the manufacturing process. The morphology of the inner surface, however, is more strongly influenced by the nature of the interface between the former and the latex. This is determined not only by the surface features of the former used, but also by the type of mould release agent that may be employed at this interface to facilitate the removal of the catheter from the former. As can be seen from the micrographs, considerable variation exists between the inner latex surfaces of different brands.

It is apparent from Figure 3 that, in the catheters studied, the PTFE-containing coating covers the contours of the outer surface but does not smooth the luminal surfaces very well, if at all. The degree of coverage of such a coating will depend on the manufacturing materials and processes employed.

In silicone elastomer-coated catheters, however, the coating appears to be much thicker, clearly covering the underlying latex so that both inner and outer surfaces are smoother. The performance of such a coating *in vivo* may depend on how well it is bonded to the latex substrate. The friction between the urethra and the outer surface of some of these catheters may lead to delamination, thereby exposing the latex substrate and shedding flakes of the coating into the urethra, providing a potential source of irritation.

Examples of hydrogel-coated catheters have not been presented here, since a micrograph of the dry surface does not correspond to the morphology that exists *in vivo*, where the hydrogel is hydrated. Cox (1987) studied such a coating in a hydrated state (using low temperature SEM) and showed that it appears very smooth. The effect of hydration is to smooth out any surface fissures.

From these micrographs it is apparent that the various catheter types have different surface characteristics which might influence their encrustation behaviour *in vivo*. For example, Axelsson *et al.* (1977) proposed that surface irregularities might act as nidi of crystal growth and bacterial colonisation. The smoothness of the outer surface is presumably linked to the ease of insertion of the catheter and the amount of friction between the catheter and the urethra during use and is therefore a desirable property. The importance of the luminal surface, however, has been ignored, although it is on this surface that most encrustation occurs, causing narrowing of the lumen and ultimately catheter blockage, and so determining catheter life *in situ* (Brocklehurst and Brocklehurst, 1978). It has been suggested that encrustation is more likely to form on rough surfaces than on smooth ones (Axelsson *et al.*, 1977), although further evidence has not been published in this regard.

Another little-studied possibility is that bacterial colonisation of catheter surfaces may be influenced by surface morphology. Sugarman (1982) showed that certain strains of gram-negative bacilli adhere better to some catheter materials than others. This subject merits further investigation, since bacterial adhesion may be influenced by other surface properties, such as surface energy, rather than by morphology.

The degree of integrity of the coating has been linked to the potential cytotoxicity of certain latex-based catheters (Talja *et al.*, 1986) which have been implicated in the formation of urethral strictures. Certainly if the latex substrate should contain cytotoxic substances, as has been demonstrated by Talja *et al.* (1986) and Wilksh *et al.* (1983), then a fissured coating might be expected to allow these to leach out into the urethra more readily than an intact coating.

The importance of the surface morphology of urinary catheters with respect to its possible role in bacterial colonisation and encrustation has received little consideration. I have illustrated the morphological differences between the generic types of Foley catheter and these should be taken into account when assessing the relative merits of the various types.

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Alternatives to Radiotherapy in the Management of Seminoma

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Summary—In a period from January 1978 to January 1989, 114 patients with seminoma have been managed, primarily in studies aimed at examining alteratives to radiotherapy. In a pilot study of single agent platinum in 27 previously untreated patients with metastatic seminoma, 82% remain progression-free and 89% alive and disease-free at 5 years compared with 81% progression-free and 88% alive and disease-free in a selected group of 16 previously untreated patients who received platinum-based combination treatment. Results from a pilot study of surveillance in 26 patients with stage 1 seminoma showed that 27% developed evidence of further disease (5 relapses, 2 second tumours) by 3 years, with all relapse patients salvaged by subsequent treatment. Because of the slow pace of relapse compared with malignant teratoma, with relapses occurring after 2 years, a pilot study was initiated to evaluate the effect of 2 courses of adjuvant carboplatin. The results to date in 25 patients suggest that with the use of modern antiemetics this regimen is as well tolerated as prophylactic radiotherapy. With a median follow-up of 16 months there has been 1 relapse subsequently salvaged by combination chemotherapy. A radomised trial is now justified to assess the quality of life and late toxicity of this approach compared with prophylactic radiotherapy.

Chemotherapy for metastatic malignant teratoma began when Li *et al.* (1960) reported complete remission in 10% of patients using a 3-drug combination containing actinomycin D; 6 years later Mackenzie (1966) reported identical results using actinomycin D alone.

Despite this observation, together with reports of a high response rate of seminoma to a single alkylating agent (Chebotareva, 1964) and the knowledge that seminoma is more radiosensitive than malignant teratoma, when Einhorn and Donohue (1977) developed the bleomycin, vinblastine and cisplatin combination for metastatic malignant teratoma, it was used to treat metastatic seminoma patients before information was available on the response of seminoma to cisplatin given as a single agent. Initially it appeared that seminoma patients did less well with this combination than teratoma patients, though this was partly a reflection of the poor marrow reserve of these patients after extensive radiotherapy (Einhorn and Donohue, 1977; Einhorn and Williams, 1980). However, because of anecdotal experience of a 10-year survivor after single agent platinum and a report that 4 of 5 patients achieved complete remission when treated with cisplatin 100 mg/m^2 weekly (3 times the standard dose), this unit has pioneered the exploration of single agent platinum as treatment for metastatic seminoma.

We now report the experience of seminoma referred to one author (R.T.D.O.) over the last decade since the advent of cisplatin-based chemotherapy and update the previously reported preliminary experience using single agent cisplatin (Oliver *et al.*, 1984; Oliver, 1987a and b) and 2 pilot studies designed to explore the impact of these observations on options for managing patients with stage 1 seminoma.

Patients and Methods

All patients with a histological diagnosis of seminoma irrespective of serum marker status referred

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between January 1978 and January 1989 and followed up until 1 June 1989 formed the subject of this analysis.

Chemotherapy protocols

From 1978 to 1980 all patients, except for 1 who had been heavily pre-treated, received bleomycin (30 mg/weekly), vinblastine (0.15 mg/kg/ × 2) and cisplatin (20 mg/m^2 daily) (BVP) for 5 days every 3 weeks for a total of 4 courses.

From 1980 to 1984 all patients received single agent cisplatin 50 mg/m^2 × 2 every 3 weeks for 4 courses. From 1984, patients who had been previously treated with radiotherapy or who had markedly elevated alpha feto-protein or chorionic gonadotrophin received a 3-day course of etoposide/bleomycin/cisplatin-based treatment according to previously reported schedules (Oliver *et al.*, 1988).

Patients without these poor risk characteristics received carboplatin 400 mg/m^2 [more recently 7 × (GFR+25)] every 3 to 4 weeks, depending on marrow tolerance.

Management of residual disease after chemotherapy

Two patients treated with combination chemotherapy and 1 treated with single agent platinum received para-aortic radiation to the site of bulky disease. Subsequently, patients with residual masses after chemotherapy were observed with repeated CT scans, although selected patients with masses >5 cm in diameter underwent laparotomy for pathological verification of complete remission.

Radiotherapy for stage 1 and 2 patients

From 1977 to 1982, any post-orchiectomy patient referred for staging who was subsequently found to be stage 1 or 2 was referred for radiotherapy (3000–3500 cGy in 20 fractions over 28 days to the para-aortic and pelvic lymph nodes) (Hope-Stone *et al.*, 1963; Blandy *et al.*, 1983).

Surveillance study

Today's practice of using tumour markers and cutting step sections of large seminomas to search for foci of non-seminoma means that stage 1 seminoma is highly selected compared with the historic material on which the justification for use of radiotherapy was based (Oliver *et al.*, 1983). As a result of the safety of surveillance in patients with stage 1 malignant teratoma having been established (Oliver *et al.*, 1982), a similar surveillance study was initiated in patients with stage 1 seminoma from 1982 to 1984. Patients were seen monthly for the first 6 months, 6-weekly for the remainder of the first year and 3-monthly during the second year. At each visit blood was taken for tumour markers dFP, hCG and placental alkaline phosphatase, and a chest X-ray was performed. CT scans of chest and abdomen were performed at 3, 12, 24 and 48 months.

Adjuvant single agent platinum studies

As a consequence of the cumulative experience of difficulty in diagnosing relapse in the surveillance study in 1984, following referral of 2 patients who had had orchiectomy delayed for more than 2 weeks after open biopsy of a testicular mass, all patients with stage 1 seminoma were entered into an adjuvant study. They received 2 courses of platinum, initially cisplatin, but subsequently carboplatin. The follow-up schedule was the same as for the surveillance study.

Anti-emetic regimen for out-patient carboplatin

Immediately prior to infusion of carboplatin, patients received oral lorazepam 1 mg, oral domperidone 20 mg and intravenous dexamethasone 8 mg. Thereafter they took oral lorazepam 1 to 2 mg, dexamethasome 4 mg and domperidone 20 mg 4-hourly for 8 to 12 h after reaching home. If they still had nausea they took domperidone 20 mg 6-hourly *prn*.

Results

Table 1 summarises the characteristics and number of patients allocated to each of the specific phase 1/2 studies; 106/114 patients (93%) remain alive and disease-free.

Table 2 summarises the results of chemotherapy for metastatic seminoma and Figure 1 summarises actuarial survival by chemotherapy regimen. The actuarial proportion alive and progression-free at 5

Table 1 Characteristics of Seminoma Patients 1978–1989

	Stage 1	*Stages 2, 3, 4*
No. of cases	62(62)*	52(44)
Median age (years)	35	37
Range	18–64	19–67
Initial treatment		
Radiation	10(10)	9(7)
Surveillance	26(26)	0
Carboplatin	22(22)	11(11)
Cisplatin	3(3)	16(13)
Platinum combination	0	16(13)

* Figures in brackets equal no. of patients currently alive and disease-free.

Table 2 Outcome of Chemotherapy of Metastatic Seminoma

	Cisplatin (n=16)	*Carboplatin (n=11)*	*Platinum-based combination† (n=16)*
Complete response (relapse)	6(0)	5(2)	9(0)
Residual mass (relapse)	10(3)	6(0)	7(2)
Treatment-related death	—	—	1*
Currently disease-free	13(81%)	11(100%)	14(88%)

* "Bleomycin lung"

† BVP n=6, BEP(5) n=4, EBCi(3) n=6. (See Patients and Methods for details of regimens).

years was 82% for patients receiving single agent and 81% for patients receiving combination treatment. One patient receiving combination chemotherapy died of 'bleomycin lung' and 1 of 2 relapses after combination therapy were salvaged by second-line chemotherapy, as were 2 of 5 relapses after single agent platinum. Thus 24 of 27 patients (89%) initially treated by single agent and 14 of 16 (88%) initially received combination therapy are alive and disease-free.

The influence of stage on progression-free survival was similar for patients who received single agent or combination treatment (Table 3). All of those who failed first-line treatment were atypical patients: 3 had elevation of hCG, 2 αFP and hCG, 1 αFP alone and 1 had an anaplastic seminoma which did not show any staining by the immunoperoxidase method using a monoclonal antibody to placental alkaline phosphatase. Four of 16 patients over the age of 45 years failed primary treatment compared with 4 of 26 under the age of 45.

Although the results using single agent or combination therapy in previously untreated patients were similar, there was a suggestion of a lower response in patients receiving single agent compared with combination chemotherapy after previous treatment. Only 1 of 5 previously irradiated patients achieved a durable relapse-free survival after single agent platinum. Two of 4 patients who had failed previous radiotherapy and 3 of 6 who had failed previous chemotherapy achieved durable relapse free-survival after platinum-based combination treatment. This difference was partly due to the higher incidence of hCG-postive patients at relapse and their poorer response to single agent platinum (Table 4).

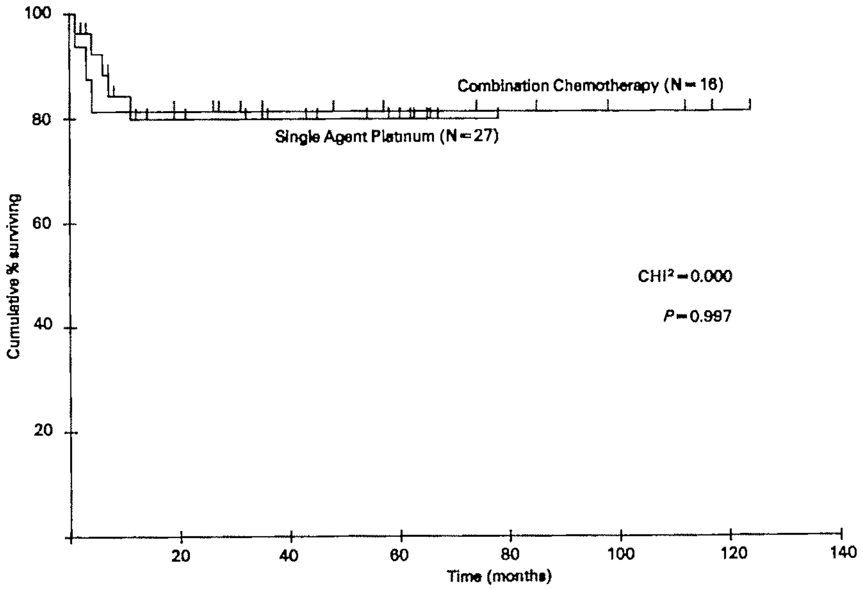

Fig. 1 Relapse-free survival of patients with metastatic seminoma after single agent or combination-based chemotherapy.

Table 3 Stage and Relapse-free Survival After Single Agent and Combination Treatment

	2b	*2c*	*3/4*
Radiotherapy	2/4	1/4	1/1
Combination	6/6	4/5	3/5
Single agent platinum	11/11	6/8	5/8

Surveillance for stage 1 seminoma

Twenty-six patients were entered into the surveillance study. Seven (27%) developed further disease (1 neck node alone, 3 para-aortic nodes, 1 common iliac node despite no previous history of scrotal violation and 2 second primary tumours) with an actuarial prediction of 75% continuous disease-free (82% metastatic relapse-free) survival at 3 years. All of those who relapsed are now alive and disease-free from 9 to 60 months (median 24) following subsequent treatment (2 after orchiectomy for a second tumour, 3 after combination chemotherapy, 1 after single agent platinum and 1 after radiotherapy).

Despite the ease of salvage, the major problem with surveillance for seminoma is the difficulty, despite the frequent use of aspiration cytology, of confirming that borderline radiological changes are evidence of relapse. Five of the 7 relapsed patients had a delay from first suspicion of relapse to confirmation ranging from 6 to 17 months (median 12). This, together with the fact that relapses have continued to occur beyond 2 years (Fig. 2) led to the studies of adjuvant chemotherapy.

Adjuvant single agent platinum treatment for stage 1 seminoma

Twenty-five patients were entered into the adjuvant study and the median follow-up is 16 months, with only 7 patients followed up for 2 or more years. To date there has been 1 relapse at 19 months in a patient whose subsequent review showed disease present between the aorta and vena cava at the time he was initially entered into adjuvant study. It would be premature to conclude that this will be the long-term result. Of more significance at this stage is the observation that using the lorazepam/dexamethasone/domperidone anti-emetic regimen it has been possible to give this treatment on an out-patient basis. The majority of patients had only 24 hours' mild nausea and less than 50% vomited, usually only once during each treatment. The acute toxicity is similar to that of patients receiving radiotherapy (Table 5), although the radiotherapy patients would have been treated with a less effective anti-emetic regime.

Of interest was the observation that the wives of 2 of the 25 patients receiving adjuvant carboplatin became pregnant 5 and 7 months after adjuvant carboplatin, suggesting the need for more detailed investigation of recovery of spermatogenesis after this treatment.

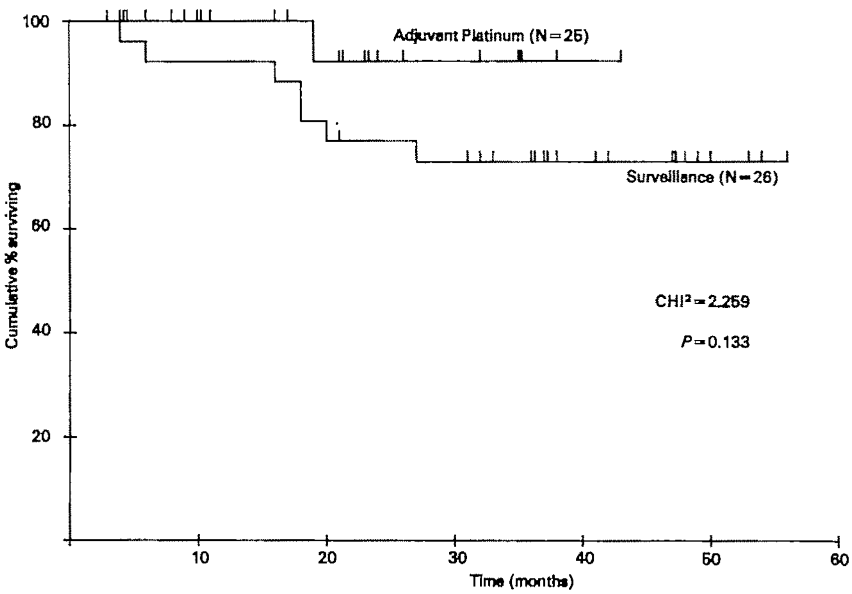

Fig. 2 Relapse-free survival for stage I seminoma patients after surveillance or adjuvant single agent platinum.

Table 4 Serum hCG and Relapse-free Survival of Patients with Metastatic Seminoma After Chemotherapy

	Previously untreated		*Post-radiotherapy*
	Platinum-based combination	*Single agent platinum*	*Single agent platinum*
hCG-negative	7/9	19/21	1/2
hCG-positive (< 150 iu/l)	4/4	4/4	0/2
hCG-positive (> 150 iu/l)	2/3	0/2	0/1

Discussion

It has long been known that a lower dose of radiation is required to sterilise regional lymph node metastases from seminoma than from malignant teratoma (Friedman, 1950). However, the relative rarity of metastatic seminoma compared with malignant teratoma and the high cure rate of the latter with combination chemotherapy (in excess of 90%) has made it difficult to appreciate that there is also a differential chemosensitivity. In addition, many of the early seminoma chemotherapy studies showed poorer survival for seminoma patients as many had been heavily irradiated before chemotherapy. In retrospect, the first indication of a differential chemotherapeutic sensitivity came from the earliest reports of chemotherapy in previously un-irradiated patients with seminoma. Although present-day criteria of response may not have been applied, Chebotareva 1964 reported 17/42 patients (41%) with a durable relapse-free survival using phenyl alanine mustard (L-sarcolysin), while Whitmore *et al.* (1977) reported 2 of 3 patients achieving durable complete remission with chlorambucil.

One patient in the present report has now been disease-free for more than 10 years after single agent platinum and the relapse-free survival rate is 82% at 5 years. This compares with 10% complete response rate of metastatic malignant teratoma reported from the original phase 1/2 study of Higby *et al.* (1974). These results, taken with the confirming report of Horwich *et al.* (1988) in seminoma patients receiving carboplatin, suggest that there can be little dispute concerning the differential chemosensitivity between seminoma and malignant teratoma, although formal proof comparing patients matched stage for stage is unlikely ever to be possible.

For the future, the critical issue is whether single agent platinum should be the standard for metastatic seminoma, or whether there is any gain from additional drugs. Review of the literature shows that cure of metastatic seminoma by combination chemotherapy ranges from 70 to 90%, suggesting little evidence of significant benefit compared to the results using single agent platinum (Table 6).

Without a large randomised trial, such as that currently under consideration as a joint MRC/EORTC study, comparing carboplatin with carboplatin plus etoposide, it is impossible to be certain. The most convincing evidence that single agent platinum is less effective than combination therapy comes from the observation that in the small number of seminoma patients in this series who have relapsed after irradiation or who have a high hCG, the results are less good than those achievable using combination chemotherapy. A similar trend is evident in the preliminary analyses of the only

Table 5 Immediate Toxicity of Stage 1 Seminoma Treatment

	No. of patients	*Vomiting/ diarrhoea*	*Leucopenia (WBC <3.0)*
Radiotherapy	10	2/3	1
Carboplatin (low dose metoclopramide)	2	2/0	0
Cisplatin (Lorazepam + dexamethasone)	3	2/0	0
Carboplatin (Dexamethasone + other)	20	8/1	2

Table 6 Survival of Patients with Metastatic Seminoma After Chemotherapy

	Stage II	*Stages III and IV*
Present series	23/24	9/13
Fossa *et al.* (1987) (23)	20/21	7/12
Wettlaufer *et al.* (1987) (24)	8/8	8/9
Pizzocaro *et al.* (1986) (25)	12/15	7/12
Peckham *et al.* (1985) (26)	19/21	7/7
Total	82/89(92%)	38/53(72%)

other study of single agent platinum (Horwich *et al.*, 1988).

This suggests that there is less margin for error in the grey zone between true seminoma and true malignant teratoma. However, there is little evidence that treating low grade lymphomas with more intensive chemotherapy reduces the risk of transformation to high grade lymphoma (Lister *et al.*, 1978). With increasing acceptance that most tumours develop by stepwise clonal evolution as a consequence of serial somatic mutation (Klein, 1979), and evidence that transformation of seminoma into malignant teratoma may be an integral part of the development of the latter tumour (Oliver, 1987a and b), it is unlikely that treatment of seminoma with high intensity chemotherapy will be of any advantage.

Given that cure of stage 1 seminoma by prophylactic radiotherapy is virtually 100%, it is difficult to make out a case for alternative approaches in the management of these patients. However, there are few really long-term follow-up studies, and those that have been done show recurrences beyond 10 years (Blandy *et al.*, 1983; Butcher *et al.*, 1985).

In addition, although Hamilton *et al.* (1986) reported a 6% incidence of chronic peptic ulcer in seminoma patients after para-aortic radiotherapy, few series provide detailed information on immediate or late toxicity. This fact, together with the observation that subclinical chronic radiation enteritis may be more frequent than previously reported (Carr *et al.*, 1984) and the stage shift produced by alterations in staging procedures, provided justification for the surveillance study. Though this approach has been as successful as prophylactic radiotherapy in terms of actual survival, the continuous disease-free survival was only 73%, with relapses continuing to occur in the third year. This has led to the exploration of alternative options. The personal experience of late relapses after prophylactic radiotherapy and the occurrence of serious hypertension in 3 of the 10 patients personally followed up after prophylactic radiotherapy were additional factors which prompted this approach.

Reports of the use of radiation for metastatic seminoma (Table 7) demonstrate that for stage 2 as well as 3 and 4, irradiation is less effective than chemotherapy (Table 6), particularly as only patients with advanced stage 2 were included in most of the chemotherapy series. This led to the conclusion that for adjuvant studies it would be more appropriate to use fewer courses of the more active agent (chemotherapy) than to continue using the less active agent (radiotherapy) if toxicity was equivalent. This led to the design of the adjuvant carboplatin study. Preliminary results seem to support the view that as far as immediate toxicity and initial disease-free survival are concerned, this approach is a viable alternative to radiotherapy. Only by a large scale multicentre randomised trial with quality of life scoring and careful monitoring of early and late toxicity, including blood pressure, will it be possible to confirm or refute this impression. The occurrence of late relapses 10 years after irradiation, the occurrence of second tumours in the contralateral testis of patients on surveillance and the early pregnancies seen in the wives of patients on the carboplatin adjuvant study, emphasise the need for follow-up for at least 10 years with careful documentation of the incidence of these events in each arm.

Table 7 Survival of Patients with Metastatic Seminoma After Radiotherapy

	Stage II	*Stages III and IV*
Read *et al.* (1983) (27)	38/67	11/32
Thomas *et al.* (1982) (28)	20/23	3/5
Ball *et al.* (1982) (29)	54/63	
Blandy *et al.* (1983) (12)	19/25	4/23
Fossa and Evensen (1985) (30)	36/42	4/23
Kennedy *et al.* (1987) (31)	146/162	26/44
Total	313/382(82%)	48/127(38%)

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Prostaglandin E_1 in Erectile Dysfunction. Efficiency and Incidence of Priapism

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Summary—Prostaglandin E_1 (PG E_1) was used for diagnostic and therapeutic purposes in 149 men with erectile dysfunction over a period of 20 months (February 1987–October 1988). The intracavernous application of PG E_1 in varying doses resulted in an erection sufficient for sexual intercourse in 79% of cases. In order to differentiate between vascular and non-vascular impotence, 5 μg PG E_1 were found to be a sufficiently high and safe dose for the first intracavernous injection. Local discomfort, ranging from mild to severe pain after injection, was recorded in 40% of patients. A significant difference in severe side effects was found between arterial, venous and non-vasculogenic impotence, the highest incidence of local pain occurring in non-vasculogenic patients. The most striking result was the occurrence of 4 cases of priapism, all in the non-vascular group, 1 of these occurring after the injection of only 5 μg PG E_1.

The first reports on the use of prostaglandin E_1 (PG E_1) for intracavernous injection in patients with erectile dysfunction were produced by Hedlund and Andersson (1985), Ishii *et al.* (1986) and Virag (1987). Unlike papaverine, or a mixture of papaverine and phentolamine, both of which are widely used in the diagnosis and treatment of erectile impotence, there are few reports on PG E_1 in this field. These rare clinical studies reported the absence of priapism (Porst, 1988; Stackl *et al.*, 1988) and the occurrence of discomfort in the penis after injection (Waldhauser and Schramek, 1988).

The aim of this investigation was to elucidate further the advantages and disadvantages of intracavernously injected PG E_1, to evaluate its effectiveness and to suggest possible reasons for the incidence of local pain.

Patients and Methods

Prostaglandin E_1 was used in 149 consecutive (but otherwise unselected) patients from our out-patient clinic who had suffered erectile dysfunction for 1 to 6 years. The patients ranged in age from 25 to 76 years (mean 53.46 ± 12.14 SD). The probable cause of erectile dysfunction was established by comprehensive multidisciplinary examination, *i.e.* intracavernous test injections of PG E_1 with increasing dosage, pharmacodynamic Doppler sonography, neurological and hormonal status and pharmacodynamic cavernography and arteriography (Schramek *et al.*, 1988); 77/149 patients (51.7%) were diagnosed as having arterial or predominant arterial failure, 30 (20.1%) as venous, 25 (16.8%) as psychogenic and 15 (10.1%) as neurogenic impotence. In 2 cases we found juvenile type I diabetes with severe vasculo-neurogenic-cavernosal incompetence responsible for the dysfunction; 11/149 patients were instructed in the self-injection technique with PG E_1. The frequency of self-injection was limited to a maximum of 2 injections/week. We now report 560 well documented self-injections of PG E_1, with a minimum of 25 and a maximum of 70/patient.

The PG E_1 (produced by Upjohn, UK), was dissolved in 0.5 ml saline solution containing 5, 10, 20 or 40 μg PG E_1, with pH and osmolarity in accordance with physiological conditions.

The injections were given by 2 urologists in the out-patient clinic, with the patient in the upright position. There was an interval of at least 2 days between each injection. The grade of erection

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achieved (1: no erection; 2: slight tumescence; 3: full volume without rigidity; 4: incomplete rigidity, sufficient for sexual intercourse; 5: full erection) and possible local side effects were recorded within 30 min of injection. The duration of the highest grade of erection achieved was recorded by means of a questionnaire. Local side effects were classified as unpleasant sensations (*i.e.* tension in the penis) (group 1) and burning sensations causing severe discomfort and prohibiting sexual intercourse (group 2).

Statistical analysis

Data concerning the incidence of side effects and diagnoses were evaluated statistically by the contingency table χ^2 test, comparing patients with or without tolerable discomfort (group 1) with patients suffering severe pain (group 2).

Results

Grade of erection

After intracavernous injection of PG E_1, 117/149 patients (79%) had an erection sufficient for sexual intercourse (73 grade 5; 44 grade 4). The doses necessary were 5 µg in 17 patients (16 with non-vascular aetiology), 10 µg in 48, 20 µg in 34 and 40 µg in 18 patients. The correlation between the main diagnoses and the doses in each patient inducing erection grade 4/5 is presented in the Figure. Other causative factors are not tabulated. In 31/149 patients, full tumescence without rigidity was induced only after the intracavernous injection of PG E_1 up to 40 µg and a venous-cavernosal insufficiency was diagnosed. One of those patients also had severe juvenile diabetes. One patient with neurogenic disease refused more than 10 µg PG E_1 (inducing erection grade 3) because of severe side effects.

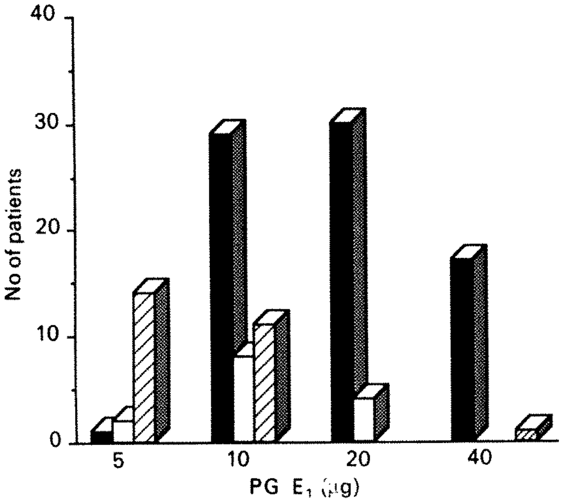

Fig. Distribution of diagnoses and dose of PG E_1 required to induce erection sufficient for sexual intercourse (grade 4/5) in 117 patients. ■ arterial, □ neurogenic, ▨ psychogenic, ▩ diabetes.

Latency between injection and achievement of erection

The median latency between application of the drug and achievement of erection grade 4/5 was 6.25 ± 3.0 min (range 3–20). There was no significant difference in latency between the groups receiving 5, 10, 20 or 40 µg PG E_1 or in relation to the diagnosis of impotence.

Duration of erection

The duration of erection ranged from 10 to 960 min (median 75 ± 48) after injection of PG E_1. As with latency, there was no significant difference between patients receiving 5, 10, 20 or 40 µg PG E_1 or in relation to the diagnoses. Priapism occurred 4 times (in 3 patients) and required treatment on 3 occasions. These patients all had a non-vascular pathogenesis (1 psychogenic, 2 neurogenic) and priapism occurred even after the injection of low doses of PG E_1, on one occasion following only 5 µg (Table 1).

Side effects

Local side effects occurred in 60/149 patients (40%) (after 5 µg in 7, 10 µg in 27, 20 µg in 21 and 40 µg in 5; not statistically significant). Group 1 side effects were observed in 36/149 patients (24%) and group 2 side effects in 24/149 patients (16%). The distribution of side effects and diagnoses is shown in Table 2. We found that most patients tolerated group 1 side effects well. The incidence of severe penile discomfort (group 2) was significantly greater in patients with non-vascular than in those with vascular impotence ($P < 0.05$).

Self-injection group

Nine of 11 patients practising the self-injection technique suffered from arteriogenic, 1 from neurogenic and 1 from mixed arterio-venogenic impotence. The duration of the self-injection period ranged from 3 to 16 months (mean 7.38 ± 4.18 SD). The following dosages were used: 10 µg in 4 patients, 20 µg in 6 and 40 µg in 1. Only 1 patient complained of group 1 side effects. Another patient stopped self-injection because of inconstant rigidity. His treatment was therefore changed to self-

Table 1 Aetiology, Dosage of PG E_1 and Treatment with Metaraminol in 4 Cases of Priapism

Patients	*Age (years)*	*Aetiology*	*Dosage (μg)*	*Duration of priapism (h)*	*Treatment*
E.J.	59	Neurogenic	20	11	Spontaneous relaxation
M.Z.	50	Neurogenic	10	13	3 mg metaraminol
J.W.	37	Psychogenic	10	16	3 mg metaraminol
J.W.	37	Psychogenic	5	7	3 mg metaraminol

Table 2 Distribution of Diagnoses and Side Effects

Side effects	*Arteriogenic*	*Venogenic*	*Neurogenic*	*Psychogenic*	*Diabetes*	*Total*
None	51	20	6	12	0	89
Group 1	16	10	2	8	0	36
Group 2	10	0	7	5	2	24
Total	77	30	15	25	2	149

injection with a mixture of papaverine and phentolamine, which resulted in adequate erections. This phenomenon of inconstant rigidity was reported by several other patients but did not lead to changes in treatment.

To date, no fibrosis or deviation of the penis has occurred.

Discussion

The use of intracavernous injection of PG E_1 in the diagnosis and treatment of erectile impotence offers certain advantages: prostaglandins are endogenous substances produced in almost every cell of the human body and act locally at the site of origin. They are not stored within cells but are rapidly released into the extracellular milieu. A single passage through the lung eliminates more than 70% of the substance (Golub *et al.*, 1975). This is why, even in patients with venous leakage, no systemic side effects have been reported in the present or other studies (Porst, 1988: Stackl *et al.*, 1988; Waldhauser and Schramek, 1988).

The fact that 79% of patients achieved a satisfactory erection (grade 4/5 in 117/149) shows the high efficiency of PG E_1. In view of the fact that 65 patients had already achieved erection after the intracorporeal injection of 10 μg PG E_1, it is concluded that 5 μg would be adequate for diagnostic purposes. Analysis of the patients who achieved erection after receiving 5 and 10 μg PG E_1, supports this conclusion: in the group with 5 μg, only 1/17 patients had mild arteriogenic failure and 16 had a non-vascular pathogenesis (14 psychogenic and 2 neurogenic); in the group with 10 μg, however, 29/48 patients showed arterial failure (Fig.). Using the intracavernous injection of PG E_1 as the diagnostic method of choice to differentiate between vascular and non-vascular impotence, 5 μg seem to be the correct initial test dose. This is of particular importance in patients with anamnestically suspected non-vascular pathogenesis, in order to avoid local side effects and priapism.

Prostaglandin E_1 itself, and not the solvent or preservative, is responsible for the high incidence of local side effects reported in 60/149 patients. We established this in a study of patients with psychogenic impotence (Schramek and Waldhauser, unpublished data), where we found dose-dependent side effects in organically healthy patients. Thus one would expect an increase in side effects with increasing dosage, but we did not observe this in the present study of patients with organic pathology. Analysis of patients receiving a higher dose (40 μg) revealed that all had marked arterial failure. Therefore the concentration of PG E_1 in the corpora cavernosa and several other factors need to be taken into consideration. Investigation of possible reasons for the incidence of penile discomfort revealed a lower incidence of severe side effects in patients with arterial failure; *i.e.* in patients with arterial pathology, the response to the activity of PG E_1 was lowered and the incidence of penile pain thereby reduced. We also found an absence of severe side effects in patients with venous leakage. The low intracavernous concentration of PG E_1 in patients with pathological venous outflow could perhaps be the reason that only group 1 effects occurred.

In 3/149 patients we observed priapism after the injection of PG E_1; 1 of these patients had 2 episodes of priapism (Table 1). In 3 of the 4 episodes

(1 after 5 µg PG E_1, 2 after 10 and 1 after 20 µg), therapy with the alpha-adrenergic stimulating agent metaraminol was necessary and in 1 case the sustained erection resolved spontaneously after 11 h. Sustained erections requiring treatment are therefore also to be expected after the intracavernous injection of PG E_1. This represents the most important finding in this study and contrasts with other reports (Porst, 1988; Stackl *et al.*, 1988) but is essential information for the patient.

In conclusion, PG E_1 is a substance that provides effective diagnostic and therapeutic possibilities. However, long-term experience, especially concerning local reactions after multiple applications, has yet to be acquired.

Acknowledgement

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Abstracts of the Proceedings of the Urological Society of Australasia, 42nd Annual Scientific Meeting, Melbourne, Australia, 1989

President: R. B. Brown
Secretary: R. M. Snow
Editor: R. J. Millard

The 42nd Annual Scientific Meeting of the Urological Society of Australasia was held at the Hyatt Hotel, Melbourne, Australia from 2 to 7 March 1989. The meeting was organised by Mr Ron Brown, President of the Society, and a committee of local urologists. Principal guests at the meeting were Professor E. Darracott Vaughan, Jr, from Cornell Medical Center, New York (Baxter Visiting Professor), Professor C. Eugene Carlton, Baylor College of Medicine, Houston (Royal Australasian College of Surgeons' Foundation visitor) and Professor J. M. Fitzpatrick (Australian Kidney Foundation Visiting Professor) from University College, Dublin.

The scientific programme featured a number of keynote presentations from the visiting professors on the major topics of neoplasia, infertility and calculus disease. The Harry Harris Oration was delivered by Mr Warwick Macky, on the life and times of Harry Harris.

The Keith Kirkland prize for the best paper presented by a trainee was awarded to Dr D. Travis for his paper on Single Stage Nephrostomy Dilatation. The Alban Gee prize for the best poster was won by Mr David Webb for his poster on the Management of Ureteroileal Obstruction by Endourology.

Letters Patent issued by the Garter King of Arms were presented to the President by Mr D. Urquhart Hay, whose hard work on behalf of the society had resulted in the grant of arms. The society expressed its gratitude to him.

The Society elected Mr Peter O. Maher, of Concord Repatriation Hospital, Sydney, to be its next president.

Bladder Cancer

Risk Factors in Superficial Bladder Cancer

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It has been suggested that following initial transurethral resection of a superficial bladder tumour, patients should be started immediately on a course of intravesical chemotherapy in order to decrease the recurrence rate and to prevent the possibility of future invasion through the lamina propria and into the deeper layers of the bladder. It is known that although the recurrence rate is high in superficial bladder cancer, the rate of invasion is very low and the overall survival rate is high.

A number of studies have shown that in patients with superficial bladder cancer there exists a "poor risk" group who are more likely to develop multiple recurrences or invasion. It is clear from a large series from Meath Hospital, Dublin, that the natural history of a particular tumour can be predicted by the recurrence pattern of a particular tumour. Although the overall incidence of recurrence was 46%, amongst the patients who returned at 3 months for first cystoscopy and had no recurrence at that visit, only 21% later developed a recurrence. The size and multiplicity of the initial tumours also had a significant effect on the recurrence pattern, as did the age of the patient at the time of diagnosis, the smoking habits of the patients and also the flow cytometric patterns of DNA content of the initial tumour.

BCG: Indicators of its Mechanism of Action

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Seventeen patients with transitional cell carcinoma of the bladder (12 carcinoma *in situ* and 5 uncontrolled papillary lesions) were treated with Pasteur strain BCG therapy. Each was given a 6-week course commencing 2 weeks after biopsy. One pathologist assessed all biopsies and cytology before and after treatment. Endoscopic assessment was made before, immediately after, and 6 weeks after treatment. At each endoscopic assessment further biopsies were taken and snap frozen for immunoperoxidase staining with a battery of monoclonal antibodies to immune cells. The aims were to ascertain the immune cellular response to BCG before and after treatment and to determine any difference in cellular response between successful and failed therapy.

Of the 17 patients, 8 failed initial treatment and 9 had a complete response, defined as no malignancy endoscopically, histopathologically or cytologically. The results of immunoperoxidase staining of the bladder biopsies before and after BCG therapy demonstrated an increase in total T cell numbers, macrophage numbers and organisation into granulomata, an increase in the T4–T8 ratio, and a slight increase in the B cells. No change in natural killer cell population was seen.

In patients who had a complete response compared with those who failed therapy, there was an increase in macrophage numbers and granulomata, and a ratio of the T4–T8 cells which more approximated 2–1. There were no consistent differences in the B cell population.

This study demonstrated an enhanced local immunological response after BCG, especially in those patients who had a complete response. This lends further evidence to the immunological basis of mechanism action of BCG.

Transferrin Receptor Expression and Tumour "Recurrence" in Superficial Bladder Cancer

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Sixty-five patients with superficial bladder carcinoma were followed up for 2 years with respect to new occurrence formation. The transferrin receptor status (TFR) of the initial tumour was recorded and proved to be a highly significant predictor of tumour "recurrence". Nine of 24 patients with TFR – ve tumours had less than 3 "recurrences", 6 of these having only 1, in the 2-year period. Thirty of the 41 TFR + ve tumour patients had "recurrences" during this time, 20 patients having more than 1 "recurrence". Voided urine cytology at the time of presentation was also found to be predictive in relation to further tumour formation.

Immunocytochemical Demonstration of $p21^{ras}$ in Normal and Transitional Cell Carcinoma Urothelium

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Activation and/or over-expression of the protein product of the ras gene family ($p21^{ras}$) has been implicated in the development of various cancers, including bladder carcinoma. We have used the anti-$p21^{ras}$ monoclonal antibody, RAP-5, to assess the level and pattern of expression in formalin-fixed, paraffin-embedded tissue sections of both normal and malignant urothelium. All 14 random normal bladder biopsies and 67 of 68 transitional cell carcinomas of the urinary bladder were positively stained with the RAP-5 antibody. In normal urothelium, $p21^{ras}$ staining tended to be localised to the superficial cell layer. With increasing histological grade and/or depth of invasion of the tumour, a greater proportion of tissue sections demonstrated a staining pattern which was more uniform with respect to the different epithelial cell types. Serially diluting the primary antibody did not reveal any significant differences in the staining patterns observed. Despite the change in staining with increasing grade, these results suggest that $p21^{ras}$ expression by itself is not a useful indicator of the malignant phenotype.

Topical (Intravesical) Chemotherapy for Bladder Cancer

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In the United States today, superficial bladder cancers (stage Tis, Ta and T1) are managed with transurethral resection and instillation of topical chemotherapy. These tumours make up 70 to 80% of all patients who present initially with transitional cell carcinoma of the bladder and most will eventually develop a recurrence. Depending upon the stage and grade of the lesion, 5 to 55% will recur in a potentially lethal form requiring more radical therapy. Overall, only 5% of stage Ta tumours, 23% of T1 tumours and 53% of Tis tumours will progress and the mortality rates from bladder cancer in these groups are 4, 25 and 25% respectively.

Intravesical agents are used widely to minimise the risk of recurrence and agents of proven effectiveness include thiotepa, Mitomycin-C, Adriamycin and BCG. Newer treatments include instillations of interferon and interleukin 11.

Thiotepa is inexpensive, easily obtained and has a low level of toxicity, including myelosuppression in 2 to 25% of patients, which is usually mild and not clinically significant. Mitomycin-C is a larger molecule with a molecular weight of 329 daltons and is rarely absorbed from the bladder. Toxicity includes cystitis and dermatitis, which are usually easily managed. Adriamycin is also a large molecule and is not readily absorbed from the bladder; haemorrhagic cystitis occurs in 12 to 40% of patients and in 5% this requires discontinuation of the drug. BCG is used widely and is considered a first-line therapy for patients with high grade, low stage tumours, as well as those with carcinoma *in situ*.

Prospective randomised clinical trials have demonstrated a reduction in recurrence rate with the use of each of these agents. Nevertheless, there is no unequivocal proof that chemotherapy will ultimately reduce the need for more aggressive, radical therapy or decrease the risk of death from cancer. One of the most troubling and unanswered questions is whether the use of such agents simply reduces the recurrence rate of low stage, low grade tumours leaving low grade, high stage tumours to run an uninterrupted natural history.

Assessment of Intravesical Lignocaine for Out-patient Cystoscopies, Biopsies and Diathermy

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Out-patient or office cystoscopies are becoming more common and provide valuable diagnostic information. However, if lesions are discovered which require biopsy or diathermy, it may be necessary to admit the patient to hospital for the definitive procedure under anaesthesia. The aim of this study was to determine if, with the instillation of intravesical lignocaine, it was possible to perform adequate biopsies and diathermy of superficial bladder tumours.

The procedure involved the insertion of 10 ml of lignocaine jelly into the urethra. Through a fine catheter, 40 ml of 1% lignocaine were instilled and left in the bladder for 10 min. Cystoscopy was performed using a rigid 21F instrument and any suspicious lesions were biopsied. If diathermy was necessary, this was performed either with the roller ball (24F) or Bugby electrode (21F). The surgeon's and patient's satisfaction were recorded on separate sheets.

Sixty patients were studied. Of 26 patients who had cystoscopies alone, only 2 would not have the procedure performed under local anaesthesia again. Biopsies were performed on 23 patients and 11 had diathermy of superficial TCC. Three patients in each group were not satisfied with the procedure, the patients who required diathermy needed general anaesthesia.

This study demonstrates that cystoscopies with biopsies and diathermy of superficial tumours can be performed as an out-patient procedure.

Role of MVAC (Methotrexate, Vinblastine, Doxorubicin and Cisplatin) in the Treatment of Patients with Transitional Cell Carcinoma of the Bladder

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Multi-drug chemotherapy for patients with advanced TCC of the bladder has opened a new dimension in the treatment of these patients, who previously had an extremely poor survival rate. Our follow-up study (*J. Urol.*, **139**, 461, 1988) revealed complete and partial remission in 69% of 83 adequately evaluable patients with node-positive or metastatic disease. Complete remission (CR) was achieved in 37% of patients, with 17 of 31 CR patients surviving 26 to 49 months.

Problems included drug toxicity, central nervous system relapse, failure in non-transitional cell lesions, later development of Tis and clinical understaging of 24%. The problem with understaging is particularly important if bladder preservation is contemplated or MVAC is used in a neo-adjuvant setting.

Neoplasia

Radical Surgery for Extensive Local Disease in Renal Carcinoma

J. M. Fitzpatrick, P. Gillen, M. K. O'Donohoe and J. M. Smith
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Considerable controversy has existed in the past as to the advisability of extended radical surgery for the management of nodal metastases and vena caval extension in renal carcinoma. It seems clear that past series may have failed to take into account the exact prognostic significance of lymph node involvement, extension into perirenal fat, vena caval involvement and their separate effects on the patient's prognosis. It is likely that nodal disease may respond to radical surgery, although the value of an extensive nodal dissection is questionable.

Radical surgery for vena caval involvement is associated with a low operative mortality rate, with a mean of 4.5% over the last 412 cases reported in the literature. Survivals of 3½ and 4½ years following "super-radical" surgery for atrial extension of tumours have been reported. At the Mater Hospital 12 patients have been treated for renal carcinoma with vena caval extension between 1979 and 1986; 7 are still alive, with a mean survival of 24 months. The surgical technique used did not involve cardiopulmonary bypass, although the advantages of this system are well recognised and it is advised that a bypass team should at least be on standby for this procedure.

Renal Carcinoma Invading the Suprahepatic Inferior Vena Cava

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Renal carcinomas commonly have direct venous invasion and in 5 to 10% of cases the tumour thrombus invades the lumen of the inferior vena cava. The technical difficulties of operative removal are increased with extension of the thrombus to the suprahepatic portion of the inferior vena cava, due to the necessity to control the inferior vena cava superior to the liver, and either above or below the level of the diaphragm. In addition, there are problems in the control of hepatic venous drainage.

In 5 cases such tumours have been excised using a combined thoracoabdominal approach using median sternotomy. Removal of the tumour thrombus combined with radical nephrectomy was successful in all cases, with good quality of survival and no operative mortality.

One patient has survived more than 4 years since operation with no sign of tumour recurrence.

Flow Cytometric DNA Analysis and Prognosis in Renal Carcinoma

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Several grading systems are currently used in an attempt to predict the outcome of individual cases of renal carcinoma. However, there is no universally accepted grading system and many of the tumours follow an unpredictable course. This study was undertaken in an attempt to determine if measurement of DNA ploidy is of prognostic value.

Between 1958 and 1980, 180 cases of renal carcinoma were seen and, of these, 137 underwent some form of surgical treatment and were available for review. Stage and grade were assigned to the review cases and each specimen was submitted for flow cytometric DNA analysis.

There were 75 diploid and 62 aneuploid tumours with 5-year survival rates of 78 and 21% respectively. When analysed by stage and grade, the presence of aneuploidy was shown to confer a significant adverse prognosis which was independent of the other variables.

The addition of cytometric DNA analysis to routine histological assessment will provide the clinician with a more precise prognosis than has been achieved previously.

The Establishment of a National Programme for Testis Cancer

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The modern management of testis cancer in specialist units yields exemplary cure rates; it is not known, however, whether these results are reproduced in a nationwide setting and the disease has not been studied in this broader context. The Irish Testis Tumour Registry has complete registration of cases since 1980, which confirms that national monitoring is feasible. Epidemiological studies have not solved the unknown aetiology of testis cancer but new associations were identified. A marked increase in mortality rates indicates a growing problem in Ireland and contrasts with elsewhere. Our pattern of disease is different and Irish patients are a high risk pathology group. Reviews of management confirm the choice of specialist treatment for each stage of disease but overall national results were less favourable than specialist units. This emphasises the need for attention to detail throughout management and the results reflect the lack of organisation of treatment on a countrywide scale. There is considerable delay in patients' presentation, leading to advanced disease and reduced prognosis. This is due to poor public awareness of testis cancer and self-examination techniques. On the basis of these results the registry has embarked on a national strategy to combat testis cancer, including national management protocols and medical and public health campaigns.

Testicular Self-examination—is it of value?

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Over the last 30 years there has been a marked increase in the incidence of testicular cancer in New Zealand. In parallel with this has been an increasing demand from patients for greater information about medical illness and greater participation in their own well-being. This study was undertaken to assess the potential benefit of testicular self-examination in the prognosis of patients with testicular tumours.

All patients with testicular cancer treated at Wellington Hospital between 1976 and 1985 were reviewed. This included 40 seminomas and 39 non-seminomatous tumours. The mean length of history to presentation was 7.4 months, with 28% of patients delaying 6 months or more. The 5-year survival rate for seminoma was 97% and for non-seminoma 82%.

Analysis showed that both length of history and size of tumour had no effect on stage of tumour at presentation. However, there was a significant correlation between size of tumour and length of history ($P = 0.018$). The regression curve shows that most tumours are noticed at a relatively constant point in their growth.

This would suggest that it is not the recognition of the growing testis that is the problem but rather the significance of the finding. Public awareness of the condition is likely to be more important than testicular self-examination.

Prostatic Disease

The Effect of Ageing on the Guinea Pig Prostate

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The aim of the study was to examine the morphological and compositional changes of the prostatic stroma occurring during the normal ageing process. These studies were undertaken in the guinea pig since this animal, as with man, has a considerable fibromuscular stromal component of the prostate.

During pubertal maturation, animal body weight increased until maturity was reached. In parallel, prostate gland weight steadily increased to maturity. Thereafter, body weight and prostate weight remained constant. The fibromuscular stroma maintained its proportional content (60% of prostate weight) during adolescent/pubertal development, but then proportionately decreased during the glandular proliferation leading up to maturity. During the senescent phase, the proportion of stroma increased to 75% as the glandular acini atrophied. Histologically, the prostate of the aged guinea pig (2 years plus) demonstrated features characteristic of benign prostatic hyperplasia in old men, *viz.* extensive stromal hyperplasia, fibrosis and prostatitis.

As the weight of the prostatic stroma increased during adolescent development, the total stromal content of glycosaminoglycan and collagen increased in parallel. However, in terms of concentration per unit weight of the stroma, these components of the extracellular matrix fell progressively through the pubertal period. Quantitative analysis using stereomorphometric techniques indicated that there was a simultaneous 6-fold decrease in stromal cell density. Ultrastructural morphometric studies demonstrated that this decrease was mainly due to an increase in size of the smooth muscle cells, which account for 95% of the cellular component of the fibromuscular stroma.

Administration of exogenous sex steroid hormones to prepubertal castrates indicated that the enlarged, differentiated post-pubertal smooth muscle cell phenotype was dependent on the presence of both androgen and oestrogen. Oestrogen administration unopposed by androgen resulted in significantly elevated deposition of both glycosaminoglycan and collagen.

These studies indicated that the proportion of stroma, the smooth muscle cell component and the extracellular matrix components of the stroma are subject to the influence of both androgens and oestrogens.

Medical Management of Benign Prostatic Hypertrophy

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Patients with symptomatic BPH are generally treated by transurethral or open prostatectomy. Approximately 300,000 prostatectomies are performed in the United States each year and care of patients with BPH occupies about 30% of the activity of a urologist. The total cost of this endeavour approaches 2 billion dollars a year. Accordingly, new strategies are evolving for the medical management of BPH.

Two approaches have reached clinical trials. First, it has been demonstrated that the administration of an LH–RH antagonist will transiently reduce prostatic size by about 30%. A multicentre trial is under way to evaluate an oral potency-sparing drug which blocks the enzyme 5-alpha reductase, thus lowering dihydrotestosterone. The second approach does not attempt to reduce prostatic size but reduces prostatic tone by alpha adrenergic blockade. Our studies support the concept that $\alpha 1$ receptors in the prostate are more important than $\alpha 2$ receptors in maintaining prostatic tone.

It will be important in the future for the urologist to be knowledgeable in the different strategies which can be offered to the patient with BPH.

Current Morbidity and Mortality of Transurethral Prostatectomy

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To determine the current morbidity and mortality rates of transurethral prostatectomy, a national co-operative retrospective study was undertaken. Thirteen participants submitted their most recent 300 consecutive cases (total 3900). For each case 223 items were evaluated and submitted for computerised analysis.

The mean age was 69 years; the average weight resected was 22 g and the surgical mortality rate was 0.3%. The intra-operative and immediate and late post-operative complications were less than 2%. However, a significant percentage of patients (12%) had an important pre-existing medical problem, *e.g.* prior myocardial infarction.

Transurethral prostatectomy is associated with a very low morbidity and mortality rate, even though a significant number of the patients presented a higher surgical risk because of pre-existing medical problems.

Out-patient Retrograde Balloon Dilatation of the Prostatic Urethra

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Recent cadaveric, animal and case reports of balloon dilatation of the prostate have aroused interest in this technique as an alternative to transurethral resection. This study reports a prospective trial of transurethral balloon dilation (TUBD) designed to evaluate the technique and results by a combined urological and radiological team. Eight patients were selected from the waiting list and evaluated by IVU, questionnaire, retrograde urethrography (RGU), cystometry, voiding flow studies (VFS) and panendoscopy. Patients with stricture, cancer or median lobe hypertrophy were excluded.

The TUBD was performed in the radiology department as an out-patient procedure under minimal sedation and antibiotic cover. Preliminary RGU delinated the external sphincter and the balloon in the urethra was dilated to its full diameter of 28 mm and maintained for 15 min under image intensifier control to confirm accurate placement. The patient was discharged home with a 20 F Council catheter which was removed the next morning and a repeat RGU and MCU performed. The patients were followed up every 6 weeks, then 3-monthly for 12 months by VFS, questionnaire and urological clinical evaluation.

All patients achieved an early subjective and VFS improvement. At 3 months, all of the VFS estimations had returned to their pre-dilatation pattern. Despite this, only 1 patient felt he had not been helped by TUBD and none felt worse as a result of the treatment. These results justify further study of TUBD.

A Comparison of Bladder Neck Incision and Transurethral Prostatic Resection for Bladder Outflow Obstruction in the Presence of Minimal Prostatic Enlargement

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Between 1978 and 1988, bladder neck incision (BNI) was performed in 118 patients for obstruction. These patients were compared with a similar group of patients who underwent transurethral resection of under 10 g of prostate (TURP) over the same period. In both groups we studied selected patients considered to have minimal prostatic enlargement (< 10 g) with prominent bladder necks and small lateral lobes. Peri-operative data were studied by means of a retrospective case record review.

Both operations were safe, with low morbidity and mortality. BNI was significantly better than TURP in terms of shorter operation time (Chi-squared test, $P < 0.016$), shorter duration of catheterisation ($P < 0.004$) and lower incidence of post-operative infection ($P < 0.03$). Over the follow-up period, 30 BNI and 43 TURP patients died from pathology unrelated to their surgery. The remaining patients were studied by postal questionnaire, to which 59 BNI patients and 86 TURP patients responded. No significant differences existed in symptoms between the 2 groups but a higher symptom score was noted in the BNI group. The 16.9% re-operation rate in a 10-year period in the BNI group was significantly less than the 22.0% in the TURP group ($P < 0.03$). Initially favourable patient assessment of their procedure by both groups (> 80% patient approval) fell significantly over 10 years in the BNI group but not in the TURP group.

Prognostic Features of Localised Prostatic Cancer and Ultrasonography in Staging the Disease

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Prostatic cancer is one of the most predictable neoplasms when properly characterised by its important prognostic features. These include stage, grade, serum acid phosphatase level, the presence of obstructive voiding symptoms and the status of the pelvic lymph nodes on pelvic lymph node dissection. Multivariant computer analysis was performed to determine the relative importance of each variable in determining the time to recurrence after treatment with definitive radiation therapy (pelvic lymph node dissection, implantation of radioactive gold seeds and external beam irradiation). Other prognostic variables included in the analysis were the age of the patient, the serum alkaline phosphatase level and the type of initial biopsy (whether needle biopsy or TURP).

Analysis showed that the most important prognostic feature of localised prostatic carcinoma was the presence or absence of positive lymph nodes. All other factors being equal, if the lymph nodes were positive the risk of recurrence per year of follow-up was 3.27 times greater for patients with positive nodes than for patients with negative nodes. Even in the presence of single microscopic positive nodes the prognosis was poor. Although 33% of patients with a single microscopic node remained free of disease at 5 years, by 8 years 95% of such patients showed evidence of recurrent tumour.

Other prognostic factors in descending order were grade of the tumour, serum acid phosphatase level, the presence of obstructive voiding symptoms and clinical stage of the tumour. Transurethral resection of the prostate prior to treatment did not influence the risk of recurrence or the ultimate mortality rate from prostatic cancer.

Transrectal ultrasonography was performed in 70 patients prior to radical prostatectomy for localised prostate cancer and the images obtained were compared retrospectively with the histological features of the surgical specimens. In 42 cases (60%), an area coresponding to the tumour could be appreciated as a hyperechoic area on the sonogram. In only 1 case did the tumour appear hypoechoic. In the other 27 cases (39%), the area of the tumour could not be clearly differentiated sonographically from the surrounding tissue. The pathological diameter of the smallest tumour visualised sonographically was 4.4 mm. A statistically significant correlation existed between tumour echogenicity and both tumour size and Gleason grade. There was linear correlation between the size of the tumour as measured by ultrasound and the actual size, with ultrasound approximately 75% of the actual size of the tumour. Of 25 non-palpable tumours, 9 (36%) were visualised on ultrasound; of 45 palpable tumours, 11 (21%) were visualised on ultrasound.

Although most clinically recognised tumours can be seen sonographically, these tumours tend to be larger, less well differentiated and palpable. These features favour the use of sonography for staging/monitoring established cancers but limit its value for early detection and screening.

Gleason Grading and Nucleolar Organiser Region Proteins in Prostatic Carcinoma

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The outcome of patients with prostatic carcinoma is varied. Gleason grading is currently used to predict tumour behaviour and aggressiveness. Nucleolar organiser regions (NORs), which are loops of DNA encoded for ribosomal RNA production, reflect cellular proliferation and may distinguish benign from malignant tissue. The purpose of this study was to compare the efficacy of Gleason grading and NORs as predictors of outcome in prostatic carcinoma.

In 45 patients with prostatic carcinoma and 10 patients with benign hypertrophy, NOR scores were significantly increased in the malignant group compared with the benign group (6.6 vs 2.8, $P<0.05$). The sensitivity, specificity and predictive value of Gleason grading and NOR scores were compared individually and in combination for the development of metastases.

	Gleason (%)	*NOR (%)*	*Gleason + NOR (%)*
Sensitivity	96	71	83
Specificity	41	74	63
Predictive value	73	74	83

These data indicate that Gleason grading may be complemented by the addition of NOR scores which enhance predictive value. The combination of Gleason grading and NOR scores provide a better prognostic index than either test alone in prostatic carcinoma.

Role of PSA in Prostatic Cancer

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Prostatic specific antigen (PSA) is a single chain glycoprotein confined to the cytoplasm of acinar and ductal cells of normal and pathological prostatic tissue. Both monoclonal and polyclonal assays for PSA are currently available, so a clear understanding of methodology and normal values is mandatory. Immunohistochemical staining techniques using PSA are extremely useful in diagnosing metastatic carcinoma of the prostate, although prostatic acid phosphatase (PAP) staining should also be done. At present, PSA is not useful in screening patients for prostatic cancer because 20 to 50% of patients with cancer will not be identified (local disease) and about 20% of patients with BPH have elevated levels. Also, PSA is not useful in staging patients, especially with regard to the extent of local disease. It appears most useful to follow patients for reappearance of disease after treatment.

Transferrin Receptor Expression in Prostatic Carcinoma

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Transferrin receptor (TFR) expression has been observed as a marker of cellular proliferative activity. It has been noted previously to be present in sufficient density to be identified by light microscopy in a variety of human malignancies. The aim of this pilot study was to determine the TFR status of prostatic carcinoma and attempt to relate this subsequently to natural history.

Specimens were obtained from 22 patients with previously untreated prostatic carcinoma and 25 patients with benign prostatic hypertrophy. Immunoperoxidase stains using the monoclonal antibody OKT-9 to identify TFR were performed in addition to routine histopathological examination.

The specimens of BPH showed a consistent staining pattern for TFR with fine regular staining of the basal epithelial surfaces. By contrast, the malignant specimens showed a marked increase in intensity and irregularity of staining and several staining patterns evident. These patterns of staining were related to the incidence of bony metastases at the time of presentation.

The results demonstrated that TFR expression was altered by malignant transformation in prostatic tissue and that the pattern of staining may prove subsequently to serve as an objective index of natural history prediction.

Residual Tumour after TUR: Pathological Features of Stage A Prostate Cancer in Transurethral and Radical Prostatectomy Specimens

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Twenty-nine patients with stage A prostate cancer underwent radical prostatectomy. The diagnosis of prostate cancer was made on pathological examination of prostate tissue obtained by transurethral resection (TUR) of a clinically benign gland. The entire TUR specimen was examined histologically. The weight of the resected specimens ranged from 7 to 110 g (mean 19). The percentage of the cut sections of the TUR sections of the TUR specimen replaced by tumour ranged from 0.2 to 50% (mean 14). Based on Johns Hopkins criteria, 11 patients had stage A1 ($<5\%$ cancer, Gleason sum <7) and 18 patients had stage A2 disease.

Radical prostatectomy specimens were examined by the whole organ step-section technique and tumour location was carefully mapped. The volume of residual prostate tissue and cancer in each specimen was estimated using these maps. The mean volume of residual prostate tissue was 22 ml. Residual invasive cancer (mean volume 2.0 ml) was found in all cases except 1, which showed severe intraductal dysplasia. Residual cancer was frequently multifocal (89%), anterior (84%) and peripheral (100%) and extended distal to the verumontanum in 63% of cases.

Despite a good correlation between the percentage of tumour in the TUR specimen and tumour volume in the radical prostatectomy specimen ($r=0.66$, $P<0.001$), 3 patients with stage A1 disease had residual tumour volumes >2 ml and 2 patients had extension of tumour through the prostatic capsule.

These data demonstrate that a large volume of prostate tissue remains after TUR and that in stage A prostate cancer this tissue almost invariably contains residual invasive cancer. Since residual cancer tends to be multifocal, to be located peripherally in the gland and to extend distal to the verumontanum, repeat TUR is unlikely to excise all remaining cancer, even in stage A1 disease.

Calculus Disease

Single-stage Nephrostomy Dilatation: an Experimental Study

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The creation of a percutaneous nephrostomy (PCN) track involves the serial exchange of dilators (Amplatz, balloon) or sequential telescoping of coaxial metal cylinders. Multiple passages of dilators prolong the procedure, increase the risk of guide wire displacement (especially in small kidneys and difficult access situations where only a few mm of guide wire are in the kidney) and allow bleeding in the interval during dilator exchange. The minimisation of bleeding is of extreme importance in paediatric PCN. This report describes the development of a new single stage dilator (SSD) for adult and paediatric use in a canine model and its comparison with the Amplatz, balloon and metal dilators.

In 20 kidneys, 22 and 24 F tracks were created under general anaesthesia at open surgery from the maximum renal convexity. Sixteen were evaluated immediately, 2 at 48 h and 2 at 6 weeks by video and still macrophotography, cast angiography, corrosion casting, serial sectioning and intravenous urography.

All 4 methods of dilatation were proven to be safe and none caused significant renal parenchymal or arterial damage. The exchange systems allowed considerable oozing of blood between removal and reintroduction of dilators. The SSD was the simplest and fastest technique and gave the most stable, tamponaded track through the renal parenchyma.

Management of Calculi in Caliceal Diverticula

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Caliceal diverticula (CD) containing calculi are uncommon. This study presents the results and techniques in 14 patients (7 men, 7 women) treated for complicated CD-containing stones. The calculi averaged 1.5 cm in diameter (0.6–3.0), were single in 8 cases and associated with upper or middle pole calices in 11 (10 left, 4 right). Thirteen patients were managed primarily by a one-stage percutaneous nephrolithotomy (PCNL) with endoscopic division ($n=7$) or dilatation ($n=6$) of the infundibular stalk to the renal pelvis or calix. Percutaneous access to the cavity was gained via a direct target puncture ($n=9$), "Y" puncture from a parallel calix ($n=3$) or along the CD stalk via the neighbouring calix ($n=1$). The 24F track entered the body above the eleventh rib in 4 and twelfth rib in 7 patients.

The connection was splinted for 5 days by a 22F nephrostomy which was held in position by an internal ureteric catheter. In all patients the stones were cleared.

One supra eleventh rib puncture created a pneumothorax which resolved with conservative management. Another patient developed post-operative sepsis and later re-formed a calculus, necessitating partial nephrectomy. Another patient with a 6-mm stone in a non-dilated CD was treated by ESWL alone with clearance of 50% of the stone mass. Neither he nor the patient having the partial nephrectomy achieved a sustained symptomatic response. The remainder are all free of stones, symptoms and infection with a minimum 3-month review (average

14, range 3–23). Follow-up IVU demonstrated impaired drainage with decreased size of CD in 5 patients, 3 obliterated and 3 unchanged.

This series demonstrates that percutaneous surgery can successfully clear calculi from CD and in most cases correct or remove the underlying aetiology.

Can Hyperuricosuria Promote Calcium Oxalate Urinary Stone Formation?

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The widely held notion that urate fulfils a causal role in calcium oxalate urolithiasis is still without sound scientific foundation. In 1970 Kallistratos reported that the addition of urate to urine salted out calcium oxalate. The aim of this study was to confirm these findings at physiological urate concentrations using human urine and to characterise the crystalline material deposited.

Urine from 109 healthy men was centrifuged at 10,000 × g, followed by 0.22 µm Millipore filtration. A filtered solution (0.22 µm) of sodium urate was added to the urine so as to increase its final urate concentration by approximately 3 mM. Controls were treated with NaOH to give the same final osmolality and all samples were adjusted to the original native pH. The metastable limit of each urine was measured by titration with oxalate and the response to a standard oxalate load in excess of this limit was quantified using a Coulter counter.

Addition of urate raised the median urate concentration from 2.3 to 6.1 mm (Wilcoxon signed rank sum test; $P<0.01$), decreased the median metastable limit from 125 to 66 µmol of oxalate ($P<0.01$) and trebled the median amount of calcium oxalate deposited from 3500 to 10,500 $\mu m^3/\mu l$ ($P<0.01$).

In all cases, scanning electron microscopy revealed the exclusive precipitation of calcium oxalate monohydrate crystals, and those deposited in the presence of added urate were markedly smaller, more numerous and more highly aggregated than those occurring in its absence. Analysis of the crystals deposited from the urines enriched with urate, using infra red, wet chemical, X-ray crystallographic and 14C-urate radiochemical techniques, demonstrated the complete absence of urate. These findings exclude heterogeneous nucleation as a likely cause for the promotory effect of urate.

These results constitute the most convincing evidence yet obtained that hyperuricosuria may be a powerful promoter of calcium oxalate stone formation. It is concluded that the salting out of calcium oxalate by dissolved urate at physiological concentrations may explain the apparent association between urate and calcium oxalate urolithiasis.

Clinical Experience with Urolithiasis in Childhood

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Urolithiasis in children is a widely varying geographic disease seen primarily in underdeveloped countries. The large centres in the United States treat only a few new cases per year and the 31 children who presented with stones between 1981 and 1988 have been reviewed. Ages ranged from 3 months to 15 years with an equal male to female ratio. A limited metabolic investigation was performed in 13 of the remaining 23 patients. Six were found to have low 24-h urinary volumes with increased urinary calcium levels. Two patients were noted to have low citrate levels, 2 patients were identified as having cystinuria and the remaining 2 had no abnormalities and were termed idiopathic. In addition, 2 patients had frusemide-induced nephrocalcinosis with resolution of tubular calcifications upon cessation of frusemide. Stone analysis in 13 patients revealed either a mixed stone composed predominantly of calcium oxalate (10) or struvite (3).

Treatment was similar to that of adult patients. Prior to 1985, standard surgical procedures were performed. Since 1985, ESWL has been employed in 9 of 15 patients ranging in age from 3 to 15 years. Eight of 9 patients were successfully treated with 1 procedure. The remaining patient had bilateral stone disease and will require a second treatment.

Complications of Ureteropyeloscopy

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Ureteropyeloscopy has made the supravesical urinary tract accessible to endoscopic evaluation and treatment previously limited to the urethra and bladder. While ureteroscopy is an extension of endoscopic techniques used in the lower urinary tract, it is a far more demanding and potentially hazardous procedure than cystoscopy. The ureter is of small calibre and thin walled, especially in its proximal segment. It is therefore vulnerable to trauma at any stage of endoscopic intervention, from the introduction of the safety guide wire to the final removal of the ureteroscope.

A review of 823 ureteroscopic interventions for stone extraction performed by experienced endoscopists at 7 different centres revealed an overall complication rate of 10.6%.

Mechanical trauma to the ureter represented 76% of the complications. Urinary tract infection or sepsis accounted for the remaining problems. While most complications resolved with conservative treatment, 17% of all complications required surgery for resolution.

The Management of Ureteroileal Obstruction by Endourology and Interventional Radiology

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The management of ureteroileal obstruction by open revision can be extremely difficult, especially in the presence of sepsis, renal failure, previous surgery or malignancy. This study presents 7 patients treated by a combined radiological and urological approach involving an initial percutaneous nephrostomy and balloon dilatation of the stenosis which was splinted by a soft catheter passing from the flank to the stoma of the conduit. This allowed the introduction of a self-retaining splint from below, or conduitoscopy and endoscopic division of the stricture. All obstructions were negotiated successfully. Three old ureteroileal strictures remained patent for 2 years after division. A patient with malignant renal failure improved to allow chemotherapy but later died of metastatic disease.

A septicaemic patient following cystectomy recovered from his shock but obstruction recurred after removal of the splint and he had an uneventful nephrectomy. Of the 2 remaining patients with benign strictures, 1 re-stenosed 4 months later and has undergone a successful undiversion and the other remains splinted, awaiting the same procedure. This series demonstrates that these minimally invasive techniques can provide safe internal diversion without a permanent nephrostomy and are excellent palliative measures for sick patients. The place of endoscopic division for benign strictures as a definitive procedure is less certain.

The Place of Endoscopic Surgery in the Management of Upper Urinary Tract Transitional Cancer

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The place of endoscopic surgery in the management of upper urinary tract transitional cell carcinoma (TCC) is controversial. Conservative open surgery in compromised renal function situations and for some highly selected low grade, low stage localised TCCs has been widely reported. We present our early limited experience in the endoscopic management of 8 patients with upper tract TCC.

In 2 cases the primary objective was palliation alone. One patient with analgesic nephropathy developed bilateral disease. The tumours were fulgurated or resected using a conventional resectoscope in 6 and a neodymium-YAG laser in 1 via a percutaneous nephrostomy. One of these patients had a TCC found incidentally at PCNL for stone removal which was too extensive to resect and he underwent nephroureterectomy. A further patient was diathermied through the ureteroscope. Four patients (2 PCN, 1 PCN+open, 1 URS) are clear of tumour at 2 years and 1 is lost to review. The patient in whom laser was employed was known to have incurable disease in a solitary kidney and renal failure. He was discharged nephrostomy-free with normal renal function after laser unobstruction but died 2 months later from residual disease.

The remaining patient developed a stenosis at the resection site at the PUJ and a second lesion contralaterally which was also resected percutaneously. The obstruction on the original side was subsequently demonstrated to be recurrent disease invading the ureteric wall.

This small experience has shown that although the morbidity of EU techniques is low, the indications for these approaches are few and should probably be confined to palliation or very select situations of compromised renal function and confirmed low grade, low stage localised disease in the presence of negative cytology and random mucosal biopsies.

Calculi in the Neuropathic Patient

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Calculi associated with a neuropathic bladder pose unique management problems. The majority are large, recurrent, infective and associated with skeletal and collecting system abnormalities. These features make the direct application of conventional forms of treatment (ESWL, PCNL and ureteroscopy) difficult.

We have treated 38 patients with a neuropathic bladder and associated renal or ureteric calculi over a 33-month period. Of these, 21 were paraplegic following spinal injury and 17 were secondary to spina bifida. Fifteen of the spina bifida patients had ileal conduit diversions. Stone size, poor drainage, stone softness, spinal deformity and sepsis made most patients unsuitable for ESWL and they required endoscopic surgery. Twenty-six (68%) were treated by endourological techniques with or without ESWL, while only 12 (32%) were managed by ESWL alone; 26 patients (68%) achieved complete stone clearance and 20 infected patients (83%) were cleared of their infection.

Pre-operative nephrostomy was required in some to drain sepsis and gain access, especially in the spina bifida patients. Since the majority of calculi were recurrent and likely to recur, complete stone removal was not always attempted, especially in complex staghorn stones. Instead, a policy of "stone control" was employed to unobstruct and debulk some very large and branched calculi to avoid excessive morbidity from the treatment itself and the remaining small calculus fragments were observed. No patient has required open surgery for stone in this group since commencing ESWL and PCNL.

Calculi in Horseshoe Kidneys

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Horseshoe kidney is the commonest fusion abnormality and is associated with obstruction, infection and calculi. Their anterior disposition, poor drainage and medial calices can make ESWL or PCNL difficult or impossible. Ten cases of calculi in horseshoe kidneys have been treated by these methods. Seven were managed primarily by PCNL, 1 had incomplete open stone clearance and failed ESWL for residual stone, and 1 had a total of 2 PCNLs, an antegrade basket extraction from the ureter and ESWL to achieve clearance. One patient who was cleared of stone developed a recurrence 18 months later which was removed by a repeat PCNL. Two patients had ESWL as primary treatment; 1 cleared and 1 has residual sand in the lower medial calix. There were no significant operative or post-operative complications.

ESWL was made difficult by the stones lying anteriorly and over bone. The dependent medial calices drain poorly. PCNL was hampered mainly by access problems from long tracks and lack of familiarity with the anatomy. Despite these handicaps, there was no significant bleeding or other complications. The 2 patients with residual fragments are both asymptomatic as these are in lower medial calices.

These cases demonstrate that although horseshoe kidneys are more complex, it is possible to remove calculi by PCNL and ESWL with a satisfactory success rate and minimal morbidity.

Initial Experience with a Second Generation Flash Lamp Excited Dye Laser

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Thirty-four patients underwent ureteroscopy for extraction of symptomatic ureteric calculi (average size 10 × 5 mm). In all cases lithotripsy was necessary and was performed with a second generation flash lamp excited dye laser. Complete fragmentation (1.3 mm particles) in 23/34 cases (67%); partial fragmentation (>3 mm) was achieved in the remaining 11 patients; 91% of patients are stone-free.

The small sized (265 microns) and flexible laser fibre may be introduced via miniaturised and flexible ureteroscopes to facilitate fragmentation of impacted calculi and calculi in small or tortuous ureters. Six distal impacted calculi that would not permit introduction of a guide wire were reached with a 7.2F rigid ureteroscope to render all 6 patients stone-free. There were no complications due to effects of the laser on the ureter. Ureteric trauma is greatly minimised by the use of smaller endoscopes which obviate the need to dilate the intramural ureter.

Universal Nephrostomy Introducer

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The need for an open nephrostomy tube is less common since the introduction of radiological intervention. However, especially for open pyeloplasty, there is a need for a single or double splint drainage system in most cases. These must be accurately inserted via a selected calix with appropriate angulation and minimal trauma or bleeding. The introduction of a nephrostomy using curved artery forceps from within or without the collecting system is fraught with the danger of bleeding and may jeopardise the whole plastic repair, especially in a kidney with a normal or thick parenchyma. Previous experimental studies of percutaneous nephrostomy have demonstrated that a blunt taper inserted into the kidney that separates the tissues will not cause significant renal damage.

Using these principles, a new universal nephrostomy introducer has been developed. This instrument has a firm, malleable soft 12F shaft with a rounded nose which easily fits in the palm of the hand or along a curved index finger to allow accurate placement into a selected site from the outer renal border or from within a calix. Following the leading taper, the introducer is widened as a soft, hollow conical tail that expands up to 28F. By placing the proximal or distal end of the nephrostomy into the flange, it can be drawn tightly through the selected entry site to produce a firm, atraumatic tamponaded drain without bleeding.

A Versatile Uretero-ileal Splint

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The ideal uretero-ileal splint (UIS) should be soft and comfortable, non-obstructing, self-retaining, exchangeable, allow radiological studies, drain each ureter separately, not interfere with surgery, be able to be irrigated and be cheap!

Commonly used splints include Jacques catheters, Silastic tubing, "Universal" or "Double-J" stents or Fogarty angiographic balloons. All have defects in use. Tubular splints will fall out easily unless sutured in and are difficult to irrigate. Angiographic equipment is expensive and tends to have only a single end hole for drainage. The ready made ureteric stents that drain so well from the kidney to the bladder rapidly block with conduit mucus and cannot be satisfactorily irrigated because of side holes along their length.

The Cope biliary stent, which has a self-retaining loop distally, was too large in diameter and the side holes became clogged with mucus. By modifying this catheter, a new splint was developed that overcame these problems. The splint has a proximal Luer lock to attach syringes or drainage bags, a 7F circumference, is 38 cm in length and self-retaining by a small loop distally which sits in the renal pelvis. Drainage is via multiple side holes 7 cm proximal to the renal pelvis, so that only unperforated tubing passes through the conduit. This allows individual renal drainage, selective injection of contrast and easy exchange over an 0.38 guide wire if necessary without mucus plugging. The splint has been used in various situations including open surgery (ileal conduit (n=4), transuretero-ureterostomy (n=1)), endoscopic division of uretero-ileal stricture (n=2) and the splinting of a conduit obstructed after DXRT (bilateral) to allow chemotherapy and removal of previously placed percutaneous nephrostomies.

Lithotripsy

Out-patient Extracorporeal Lithotripsy of Kidney Stones: 1200 Treatments

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A total of 1200 extracorporeal lithotripsies have been performed in 816 patients; 58% of the stones had a diameter of 3 to 10 mm, 41% measured between 11 and 20 mm and 1% were larger than 20 mm. The patients were treated on an out-patient basis without anaesthesia or analgesia. The mean time spent at the centre was 2 h and the mean treatment time was 46 min.

A total of 530 patients were reviewed after 3 months and 64% were stone-free. The results varied between 73% for stones <10 mm in diameter and 43% for stones >20 mm. In patients presenting with a single stone, 69% were stone-free at 3 months. The best results were obtained in upper caliceal stones (78%) and the least satisfactory results in the lower caliceal stones (68%).

The complication rate was low, with renal colic in 18% of cases and fever in 2%. Ureteric obstruction in 13 was managed endoscopically in 12 and surgically in 1. One-third of patients were re-treated without admission to hospital.

Out-patient extracorporeal lithotripsy is indicated for renal pelvis or caliceal stones <20 mm in diameter situated in a non-obstructed renal cavity, in a non-infected patient without any particular risk factors; 85% of patients are currently treated on an out-patient basis.

Extracorporeal Shock Wave Lithotripsy (ESWL) for Renal Stones Using the Lithostar Lithotriptor

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Numerous reports attest to the efficacy of ESWL in the treatment of renal calculi. Few authors have reported their experience with ESWL in the management of ureteric calculi *in situ* and controversy exists as to the role of ESWL monotherapy in the treatment of staghorn calculi. We report our early experience with ESWL in the management of renal calculi, ureteric calculi *in situ*, and as monotherapy for staghorn calculi.

Over a 9-month period, using the Siemens Lithostar Lithotriptor, 129 patients underwent 168 treatment sessions for 166 stones. The mean age was 44 years (range 2–78). In 90% of patients sedation was necessary and 8% (mostly children) had a general anaesthetic. Three patients had no sedation. Results were as shown below. Additional procedures were performed in 21 patients (16%): Dormia extraction 5, double-J catheter 9, percutaneous nephrostomy 5, open surgery 2. Complications were observed after 33 treatments (20%); ectopics 13, pyrexia 8, haematuria 6, pain 3, Steinstrasse 2 and haemoptysis 1.

It was concluded that the Siemens Lithostar is a very effective lithotriptor with a stone clearance rate of 88% at 3 months. Ureteric calculi can be successfully treated *in situ* and ESWL monotherapy is an effective treatment for staghorn calculi.

	Patients	*Stones*	*Rx*	*Shocks/Rx*	*Immediate fragmentation*	*Clearance at 3 months*
Renal	76	111	83	1793+651	75/83 (90%)	35/39 (90%)
Ureteric	35	35	39	1656+890	36/39 (92%)	23/27 (85%)
Staghorn	18	20	47	2325+1600	44/47 (94%)	5/6 (83%)
Total	129	166	168	1724+1035	155/168 (92%)	63/72 (88%)

ESWL in Large Stone Burdens

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Singapore

The effectiveness of ESWL was investigated in patients with large stone masses in their kidneys. As the definition of stone burden we used the total added length in mm of the individual stones in a kidney as measured on a standard KUB.

In a series of 94 patients, 108 kidneys with an average stone burden of 51 (range 30–114) were treated with ESWL. Of these, 12 were treated once, 80 were treated twice, 15 were treated 3 times and 1 was treated with 4 sessions. Double-J stents were inserted pre-operatively in 86 kidneys. Auxiliary measures were necessary in 10 patients who had not had double-J stents.

Forty-five kidneys became stone-free; 7 showed fragments smaller than 2 mm and were given no further treatment; 24 were lost to follow-up and the rest are scheduled for further ESWL treatment.

The complication rate of ESWL for big stones has been reduced considerably with the use of double-J stents. Staging the procedure eliminates stone size as a limiting factor for ESWL. Staghorn stones are now routinely accepted for ESWL with double-J stent *in situ* at our centre.

US Experience with EDAP LT-01 Lithotriptor

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Between March and October 1987, 212 patients with 288 stones were treated in 258 treatment sessions with the EDAP LT-01 lithotriptor; 166 patients had 1 stone and 179 patients had a single treatment. Stone size averaged 9.96 mm (range 2–30). Anaesthesia was either intravenous sedation or nothing, except for a few cases where concomitant endoscopic manipulation necessitated general or regional anaesthesia. The re-treatment rate was 21.7%. The stone-free rate was 63.4% overall but 13.6% of stones showed no change. The only complications were 2 cases with Steinstrasse.

The EDAP LT-01 is safe and effective. The low stone-free rate at first is mostly a function of the learning curve and this is borne out by the more recent data which show a stone-free rate of >80%.

Piezoelectric Lithotripsy of Renal and Ureteric Calculi using EDAP LT.01

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The EDAP LT.01 is a bathless lithotriptor using electrical excitation of piezo-ceramic crystals for shock wave generation and ultrasound as a localising medium. Between March and September 1988, 175 patients were treated for renal and ureteric calculi. The mean age was 52 years (range 8–80). Stones in the lower calix accounted for 40% and stones in the renal pelvis, lower and middle calix and ureter were of the same frequency (15% each). The mean stone size was 10 mm (range 4–30).

Most patients experienced very little discomfort (or none at all) during treatment and only 15% required slight sedation. Of the kidney stones, 98% were treated on an out-patient basis compared with 45% of the ureteric stones, which were usually pushed back to the pelvis before treatment. The mean number of treatments per patient was 1.4 (range 1–4) and the mean treatment time was 60 min. Antibiotics were administered to 40%, starting 4 days before treatment.

Within 1 month, 70% of the patients became stone-free and another 7% had residual fragments <5 mm on piezoelectric lithotripsy only. Auxiliary procedures such as ureteroscopy, percutaneous nephrolithotomy or nephrostomy drainage were required in 9%. The technique was most effective against renal pelvic stones and ureteric stones after mobilisation. *In situ* localisation/treatment of ureteric stones was only occasionally successful. No patient has so far required hospitalisation because of pain or fever but 15% have required analgesics on the following days.

Piezoelectric lithotripsy is a welcome addition to urological procedures. Ultrasound as a localising medium has proved easy to use and the system an effective, cost-effective, anaesthesia-free out-patient lithotripsy device.

Lithotripsy with the Wolf Piezolith

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Urinary stones in 300 kidneys in 290 patients were treated with extracorporeal piezoelectric lithotripsy (EPL) using the Wolf Piezolith 2300. In order to make the treatment truly intervention-free, our policy was not to perform preliminary procedures. Specifically large renal stones were treated without ureteric stenting or percutaneous stone debulking.

No patient received anaesthesia or analgesia whilst undergoing lithotripsy and 70% were treated solely on an out-patient basis. Of the patients with stones <20 mm in maximum diameter, after a mean of 2 sessions/patient, 55% were free of stone and another 35% had fragments <3 mm in size. Of the patients with stones >20 mm, after a mean of 5 sessions/patient, 15% were free of stone and another 30% had fragments <3 mm in size. Of those patients with large stones, 7% failed EPL therapy and required percutaneous stone surgery and another 18% required secondary procedures for obstructing ureteric stone fragments.

EPL is effective monotherapy for stones <20 mm but larger stones require ureteric stenting or percutaneous debulking for optimal results.

ESWL and Double-J Stents

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A total of 138 kidneys were assessed following ESWL, with and without ureteric stenting. Of these, 110 kidneys (mean stone size 14 mm) were unstented and 28 were stented. Follow-up was for a minimum of 3 months.

Stone-free status at 3 months was 76% without a stent and 71% in the stented group. Complications included Steinstrasse in 8/110 (7%) of unstented patients, of whom 2 required percutaneous nephrostomy and subsequently spontaneously passed the ureteric particles. Steinstrasse occurred despite a ureteric stent in 4/28 cases (14%); 3 required ureteroscopic stone removal and 1 required removal of the stent only. Additional complications in the stented group included significant stent-stone formation in 1/28, blocked stent and urosepsis in 1/28, while morbidity related to local pain and bladder irritation was almost universal.

The use of a ureteric stent with ESWL enables larger calculi (mean stone size 22 mm) to be treated with a stone-free rate comparable to that of smaller stones (mean stone size 14 mm). However, stenting did not prevent the development of obstructive Steinstrasse and was associated with considerable morbidity due to local irritation from the stent.

Infertility and Impotence

The Aetiology and Presentation of Ductal Obstruction as a Cause of Infertility

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Obstruction of the duct system of the male genital tract is a common cause of infertility. It occurs in 14% of men presenting in a male infertility clinic and is the cause of sterility in nearly half of all men with azoospermia. The aetiology of ductal obstruction appears to be undergoing a change. Infection is now an uncommon cause, with gonorrhoea contributing to only 5% of all cases. In its place, Young's syndrome has become the single most important cause.

The presentation may vary according to the site and nature of the lesion. If these lesions are complete and bilateral, azoospermia will be present. As testicular function is normal, testicular size and testicular endocrinology will also be normal. In men with intratesticular obstruction, the epididymis is flaccid and empty of sperm and Bayle's sign is negative. These lesions and germinal aplasia are often confused clinically. In more than 70% of patients with obstructive azoospermia the obstruction is found in the epididymis and Young's syndrome is associated with most of the patients with obstruction close to the head of the epididymis.

Bilateral congenital absence of the vas makes up 10% of cases with obstructive azoospermia and, due to the associated absence of the seminal vesicles, often presents with hypospermia and abnormal semen biochemistry, as does any obstructive lesion involving the ejaculatory ducts. Unilateral obstruction may also cause infertility and result in oligozoospermia and the presence of head to head agglutination in a TAT test. Obstruction may also be incomplete and be a cause of oligozoospermia.

There are thus different ways in which obstructive lesions of the male genital tract may present and cause infertility, so producing difficulty both in diagnosis and in management.

Micro-SPA: a Modified Sperm Penetration Assay Test for Oligozoospermic Patients and Correlation of Results with Intrauterine Insemination

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This laboratory has established a highly sensitive and controlled method for determining the fertilising potential of sperm of oligozoospermic patients using an optimised zona-free hamster ova sperm penetration assay (SPA). Compared to established standard SPA techniques, our micro-SPA method achieves a 30-fold increase in sperm penetration rates but requires only 1/10 the usual number of motile sperm. Since we need only 25,000 motile sperm per assay, we are now able to measure the sperm capacitation index (SCI; average number of penetrations per ovum) of patients who previously had too few post-capacitated motile sperm for the routine assay.

Sperm are capacitated for 2 days at 4°C and aliquots of 25,000 are centrifuged in a 400 µl microtube. Zona-free ova are added to the tube for a 3-h incubation. Since our cryopreserved semen standards limit interassay variation to 20%, we can confidently compare micro-SPA results obtained on different dates. The mean SCI obtained from 17 pregnancy-proven donors was 24.1 ± 11.1 SD. Micro-SPA results were prospectively correlated with the percentage of human ova fertilised in 17 consecutive IVF cycles. Of the 14 patients who fertilised >33% of human ova, all had an SCI >2.5 (mean 13.3), whereas of the 3 patients who had an unfavourable cycle with <17% of human ova fertilised, all had an SCI <2.5 (mean 1.3).

Our modified SPA accurately predicts IVF outcome, requires only a fraction of the sperm and is far more sensitive than conventional techniques. Thus we can now inprove our assessment of the fertilisation potential of the oligozoospermic patient. Multiple techniques of artificial insemination using husband's semen have provided varying pregnancy rates. We selected 32 couples presenting with primary infertility to undergo intrauterine insemination (IUI) to increase the number of sperm at the fertilisation site. All underwent prior evaluation, which included physical examination, semen analyses × 2, gonadotrophin levels and the sperm penetration assay using zone-free hamster eggs (SPA). Those men who demonstrated a normal semen analysis had further testing, including evaluation of antisperm antibodies and post-coital test versus the cross-mucus test.

Infertility was found to be secondary to oligoasthenospermia in 21 couples (65.6%), presence of antisperm antibodies in 7 couples (21.8%) and cervical factors in 4 couples (12.5%). Overall, 6 pregnancies (18.8%) were documented after a mean of 2.3 IUI cycles: 5 of the 21 oligoasthenospermia group and 1/4 (25%) of the cervical factor group. In the former group the SCI in the pregnancy documented group was 13.6 compared with 5.2 in those who did not conceive ($P<0.05$). The patients with significant antisperm antibodies, however, were noted to have SCIs with a mean of 16.2.

Thus IUI achieved an overall pregnancy rate of 18.8% with the greatest success in couples with oligoasthenospermia or cervical factor. SPA appears to be an accurate predictor of pregnancy outcome in those patients with oligoasthenospermia. The presence of antisperm antibodies greatly impedes the success of this treatment.

The Management of Oligozoospermia

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Clinical assessment and investigation of patients with oligozoospermia should be geared to the detection of known aetiological factors. Investigations should determine the severity and reproducibility of the defect in the patient's semen since this can provide some prognostic information regarding outcome which also depends on the reproductive status of the female partner.

Where treatable causes are found, appropriate management should be instituted. However, in 40 to 50% of cases the diagnosis is idiopathic infertility and no treatment to restore sperm count is available. Recent studies have shown that such patients can be managed by the use of *in vitro* fertilisation and embryo transfer. The requirement of only 100,000 to 250,000 motile sperm per oocyte to achieve fertilisation *in vitro* has led to the use of such sperm numbers isolated from men with oligozoospermia. Such fertilisation rates are decreased in comparison to normal (85%) and are related to whether a single defect in count, motility or morphology (fertilisation rate = 65%), a dual defect (any 2 abnormal parameters; fertilisation rate = 50%) or a triple defect (fertilisation rate = 30%) are seen on the semen analyses.

Once fertilisation occurs, the chances of achieving pregnancy are no different from those fertilised oocytes achieved with semen from normal partners. If fertilisation fails, it is possible that the technique of microinjecting a single sperm into the perivitelline space may offer a further chance for fertility.

Prostaglandin for the Treatment of Impotence

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While papaverine is the agent most widely used for the treatment of erectile failure, there have been disturbing reports about penile fibrosis associated with its use. In order to test an alternative drug, a trial was conducted to compare prostaglandin E_1 with papaverine in impotent patients.

Either 20 mg of papaverine or 5 µg of prostaglandin E_1 were injected into the corpus cavernosum of 50 men. The response was observed after 30 min by E.J.K. During the following 4 weeks the patients were asked to record their sexual activities. They were then reinjected with the alternate drug and the same protocol followed.

The resulting erection was more impressive in 66% of patients after prostaglandin and in 16% of patients after papaverine. In the remaining patients the responses were equal. The patients' subjective assessment was similar.

This study shows that in the doses chosen, prostaglandin E_1 was the more effective drug. Furthermore, prostaglandin has not so far been implicated as a cause of penile fibrosis.

Histopathology of the Epididymis in Young's Syndrome

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The commonest site of epididymal obstruction in patients with azoospermia is in the head of the epididymis, and 75% of these men have sinusitis, bronchitis or bronchiectasis (Young's syndrome). The aetiology of the condition is obscure and although muco-ciliary function is impaired, the ultrastructure and beat frequency of the cilia are normal. This suggests an abnormality of the mucus, although classical fibrocystic disease has been excluded in earlier studies.

We have, therefore, looked again at the histopathological changes in the heads of the epididymides in 46 patients with Young's syndrome and compared the findings with those seen in this part of the epididymis in normal testes and in testes removed for irreparable obstruction at the tail of the epididymis or in the vas. All patients with Young's syndrome showed plugs of inspissated degenerating spermatozoa, with prominent accumulation of lipids (demonstrated histochemically) and confined to the ductuli efferentes. This part of the epididymis is lined by a single layer of ciliated columnar epithelium and this differs from body and tail which is lined by stratified columnar epithelium. Marked accumulation of lipid is not seen in other cases of obstructed epididymis, which raises the possibility that the fundamental defect in Young's syndrome may be metabolic.

Transrectal Ultrasonography for Patients with Obstructive Ductal Disease

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Anatomical abnormalities of the vas deferens have been frequently described in the infertile male. Seminal vesicle pathology has never been reported in any large series due to the difficulty of assessing these glands in patients with vasal atresia. Transrectal ultrasonography has enabled the status of the seminal vesicles to be clearly visualised and we now test every patient with a suggestion of ductal abnormality.

Radial transrectal ultrasonography was performed in 69 patients with either azoospermia (56) or oligozoospermia (13). These patients were suspected of having ductal abnormalities because of normal serum gonadotrophins (FSH, LH) in association with an abnormal physical examination and/or low semen volumes. Sonographic findings of the seminal vesicles were divided into 5 categories by size: normal, dilated, thin, atrophic or absent. In 52 patients, 73 testes were surgically explored and the findings compared with ultrasonographic data. Complete absence of at least 1 seminal vesicle was found in 26 patients, including 9 with bilateral absence. In addition, only 14 (20%) had bilaterally normal seminal vesicles. If the seminal vesicle was "atrophic" or "absent" on ultrasonography, in most cases the surgical findings revealed that the ipsilateral vasa were absent or obstructed in the retroperitoneum and were not surgically correctable. Surprisingly, even though surgical exploration revealed no vas deferens, a "normal" or "dilated" seminal vesicle was found in 8 patients. By contrast, in 5 men with absent or atrophic seminal vesicles, the vas was patent up to an obstructed site in the retroperitoneum. Discrepancies between predicted continuity of the seminal vesicles and the vas deferens probably represent a segmental developmental defect.

Transrectal ultrasonography is a non-invasive and useful procedure to detect abnormalities of the male ductal system.

Experience with Penile Prostheses in 107 Patients

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A group of 107 patients were treated for erectile impotence by the insertion of a penile prosthesis. Patients were investigated by history, physical examination, Doppler, NPT studies, blood chemistry and the papaverine response.

The causes of impotence in this group were fractured pelvis (4), diabetes (21), Peyronie's disease (8), Ca prostate (4), vascular (12), proctocolectomy (2), alcoholism (10), priapism (2), paraplegia (1), multiple sclerosis (1), psychogenic (10) and idiopathic (32).

A total of 109 implants were used in 107 patients. The implants used were Jonas (35), AMS Malleable (27), Hydroflex (6) and AMS 700 inflatable (41). Mechanical complications requiring adjustment or replacement of the prosthesis occurred in 14% of AMS 700 operations (6/41) and 5% of Malleable implants (3/62). All mechanical complications were corrected. Infection occurred in 4 patients, resulting in removal of the prosthesis in 2.

Patient and partner satisfaction and penile sensation were excellent in over 90% of patients. Natural augmentation of the prosthesis erection occurred in 50% of patients.

Effects of a Sclerosant, Ethanolamine, on the Venous Drainage of the Dog Penis

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Cavernosography has identified a group of impotent men with abnormal venous run-off but ligation of abnormally large venous channels has failed to restore potency. A high success rate has been reported by combining deep dorsal vein ligation with injection of sclerosant into the pelvic veins draining the penis. Using the dog as an animal model, we injected ethanolamine (5 ml of ethanolamine with 5 ml of 74% Urografin solution) into the deep dorsal venous system of the canine penis. Six dogs were anaesthetised and then injected with sclerosant solution and 6 control dogs were injected with normal saline. The animals were sacrificed (IV lethibarb) 24 h, 1 week and 1 month after surgery. Venograms were performed during the injection of sclerosant solution and prior to sacrifice.

There was no instance of priapism or other side effects. At autopsy, no obvious abnormalities were noted. Histopathology showed that the sclerosant had produced occlusion in the deep dorsal system by forming intramural thrombi. Within 1 month re-canalisation of most of the veins had occurred and collateral channels were demonstrated on venography.

Ethanolamine is an effective venous sclerosant in the dog but formation of venous anastomoses was rapid. In view of the potential for the venous drainage of the dog penis to form new anastomotic channels, similar studies need to be conducted in man before advocating sclerosant therapy for impotence.

Miscellaneous

Long-term Follow-up of Colposuspension

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Recent studies of colposuspension draw attention to the incidence of post-operative failure. This study reports on continence 1 year after operation and also long-term results (average 4.5 years of follow-up).

A total of 102 patients with urethral sphincter incompetence were treated by an open technique in which the full thickness of the vaginal wall was suspended by heavy monofilament sutures placed well lateral to the urethra and tied over the rectus muscles. Fifteen patients had pre-operative detrusor instability and 20 had undergone 2 or more operations for incontinence.

Follow-up of 99 patients was available at 1 year; 21 had recurrence of incontinence within 1 year. Detrusor instability (7) and multiple previous operations (9) were the main factors associated with failure. Delayed voiding (longer than 10 days) occurred in 18% and was related to wound discomfort and poor detrusor contractility.

Of the 78 continent patients who were followed up for more than 1 year, there were 7 late failures. A Kaplan–Meier survival curve showed a probability of continence of 69% after 5 years.

Combining both early and late failures, pre-operative detrusor instability resulted in 60% failure (9/15) and multiple previous vaginal repairs and/or failed colposuspension resulted in 55% failure (11/20). In the absence of these factors, long-term continence was maintained in 90%.

Rectus Flap Colposuspension for Stress Urinary Incontinence

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Between 1981 and 1987, 21 consecutive patients presenting with stress urinary incontinence (SUI) were treated by rectus flap colposuspension. Through a Pfannenstiel incision and with the vagina prepared, the retropubic space is opened and the bladder neck located by means of a Foley catheter. Medially based flaps of anterior rectus sheath, 3 × 1 cm, are cut from the inferior margin of the incision, passed lateral to the rectus muscle and attached to the anterior vaginal wall at the vesicourethral angle using 0 prolene sutures. Suture placement is aided by elevation of the vaginal wall at the correct point with a finger in the vagina. Suction drainage for 24 h and catheter drainage for 2 days are used under cefotaxime and tinidazole cover.

Complete follow-up of all patients was obtained for a period ranging from 12 months to 7 years (mean 37 months). Eighteen of the 21 patients (86%) remained cured of SUI for up to 5 years; 3 patients had recurrences at 1, 3 and 6 months respectively. One patient relapsed after 5 years.

Twenty patients voided without difficulty when the catheter was removed at a mean of 3 days (range 2–12). Only 1 patient required a catheter for 6 weeks. No significant complications occurred. The mean hospital stay was 10.3 days (range 6–18). Rectus flap colposuspension is recommended as an open procedure for the cure of stress incontinence.

Changes in Urethral Pressure Profiles with Interferential Therapy for Pelvic Floor Weakness

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Considerable controversy exists over the effectiveness of interferential electrostimulation of the pelvic floor and the treatment of stress incontinence. In order to assess the effects of the procedure and to optimise treatment schedules, a study was undertaken on 5 consecutive patients undergoing treatment for genuine stress incontinence.

Patients with urodynamically proven genuine stress incontinence were selected for conservative treatment involving pelvic floor exercises and a course of 10 to 12 interferential therapy sessions. Before and during interferential sessions, cystometry, cough profilometry and urethral pressure monitoring were conducted using dual sensor microtip transducer catheters on all patients, each acting as their own control.

Urethral closure pressures were improved during and after the interferential treatment in 2 patients and during treatment only in 1. The urethra appeared to tire during interferential therapy in 2 patients and this effect persisted afterwards. Interferential therapy did not stimulate easily fatigued sphincters and these patients had a poor clinical outcome. In the limited follow-up to date, the stimulatory effect of interferential therapy lasts beyond the actual stimulus time. The treatment did not appear to augment a normal urethral pressure profile and further investigation is necessary to ascertain its long-term effects.

Development of the Invaginated Sleeve Technique for Continent Ileal Urostomies in Dogs

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A major difficulty encountered in establishing continent bowel reservoirs has been the construction of durable, continent stomas. One year ago we reported the development of an invaginated sleeve technique in dogs to provide continent cystostomies.

In this study of 6 dogs, the invaginated sleeve technique was performed on an isolated segment of ileum, the distal end of which was anastomosed to bladder. The invaginated tubularised pedicle graft was stretched so that it extended well beyond the proximal end of the isolated bowel segment, this protruding graft being wrapped with omentum to ensure viability.

Two dogs were sacrificed at 3 and 4 weeks with the stent in position. The other 4 dogs had the stents removed at a second procedure and were catheterised twice daily with an 8F catheter for 10 days and 5, 7 and 13 weeks respectively. Bacteriuria was present in all but 1 dog and ileal mucosa was metaplased to low columnar epithelium and replaced by urothelium in the extra-ileal parts of the grafts. Haematoxylin and van Gieson stains demonstrated little scarring in the invaginated ileal segments, implying that these tissues were well vascularised and remained supple.

No difficulty was encountered in catheterising 2 of the dogs, but 8F catheters were difficult to pass in the other 2 dogs at 10 days and 7 weeks respectively. Histologically these 2 animals had reduced luminal diameters with increased collagen in the walls of the extra-ileal parts of the grafts.

The invaginated sleeve procedure is a simple technique which uses less than 10 cm of ileum to create an effective continence mechanism and a robust catheterising tract. This approach provides another option for consideration in continent urinary diversions.

Effects of Partial Ureteric Obstruction on Renal Blood Flow

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Complete unilateral ureteric obstruction is followed by decreased ipsilateral renal blood flow (RBF) with variable perfusion of the renal cortex. Previous studies have indicated that partial ureteric obstruction (PUO) also induces changes in RBF. The effects of PUO on regional renal blood flow are unknown. We tested the hypothesis that PUO would result in alterations in regional RBF.

In 5 mongrel dogs a subcutaneous nephrostomy was established in the left kidney. The left ureter was partially obstructed for 4 weeks and then reimplanted into the bladder for a further 4 weeks. Whitaker tests were performed and RBF was assessed prior to and following ureteric obstruction and after reimplantation. Radioactive microspheres were used to measure renal blood flow. The nuclides used were ^{85}Sr and ^{57}Co and ^{113}Sn. At the end of the experiment the kidneys were sectioned and % RBF was calculated for outer (OC) and inner cortex (IC) and medulla (M).

The Whitaker tests confirmed obstruction and relief of obstruction in all animals. Results were as shown below. These results indicate that chronic unilateral PUO causes profound alterations in total and regional RBF in both kidneys. Relief of obstruction does not reverse the changes in RBF. We speculate that the altered regional RBF in the contralateral kidney may be hormonally mediated.

	% Total RBF		*% Regional RBF*					
			Left kidney			*Right kidney*		
	Left	*Right*	*OC*	*IC*	*M*	*OC*	*IC*	*M*
Before obstruction	65±8*	35±88*	71±3	26±3*	2±1	64±6*	30±5*	6±2
After obstruction	36±11	57±7	56±6	39±6	5±3	60±6	34±4	7±3
After reimplantation	30±9	69±9	42±14	44±12	6±4	63±4	33±2	5±1

* $P < 0.05$ vs post-obstruction.

Intermittent Self-catheterisation and a Catheter Storage Tube: a Review of Experience in the Neuropathic Bladder

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Fifty-six patients with various types of neuropathic bladder have been performing intermittent self-catheterisation (ISC) using a catheter stored in a tube containing glycerol and chlorhexidine. The technique involves careful cleaning and washing and drying of the catheter after each use and then returning it to the tube. When the catheter is required next it is already lubricated and ready for use. The flexible plastic tube has a screw top incorporating a spigot which holds the catheter and a screw bottom so that both can be removed once a week to clean the tube by soaking it in dilute Milton for 2 h before replenishing the glycerol chlorhexidine solution. The technique allows multiple use of the same catheter for a week.

In a prospective group of 9 patients, cultures of urine samples, urethral swabs and tube lubricant were obtained each week for 4 weeks, giving 68 samples for analysis. One clinical infection occurred. The tube cultures were sterile in 46/68 (67%). Catheter urine samples showed asymptomatic bacteriuria in 48/68 tests but 5/9 patients had sterile lubricant throughout.

In the group of 56 patients, mostly with spinal cord injuries studied for a mean 29 months (range 7–77), symptomatic urinary infections occurred in 12, urine was always sterile in 16, and asymptomatic bacteriuria was noted in 28. Complications included urethral false passage (1), stricture (1), urethral bleeding in a haemophiliac and reaction to chlorhexidine in 1 patient.

Overall, 43/56 continue to use ISC with the tube. Of 26 patients with uninhibited bladders, 19 (73%) are dry between catheters, some requiring anticholinergic agents but without significant change in urodynamic parameters. Interval continence is achieved by using the bladder capacity below that which provokes uninhibited contractions.

Of the 30 patients with areflexic bladders, 24 continue with ISC, although 2 had a colposuspension, and all are dry. Five were able to change to Valsalva to empty their bladders and 1 wished to convert to condom drainage.

ISC is a well established technique for achieving bladder emptying with good patient acceptability. The catheter tube has proved safe and cost-effective.

Changes in Urological Surgery and the Implications for Training and Manpower Requirements

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The total operating experience of 1 urologist in private and public operating was reviewed over a 10-year period. Comparison of the endoscopic and open cases showed marked changes over the decade.

The percentage of open versus endoscopic prostatectomies changed from 19 to 0.5%, despite an overall increase in numbers. The percentage of open versus endoscopic removal of ureteric calculi changed from 50 to 2% and of renal stones from 100 to 2.5%. During the same period, many other areas of open surgery also reduced. Urethroplasty in many cases was replaced by optical urethrotomy, hydrocele and epididymal cyst by aspiration and sclerosants. Other operations also under threat include pyeloplasty, ureteric reimplantation, nephrostomy, priapism shunts and renal endarterectomy.

These changes have produced significant benefits for the patients, with reduced bed stay, fewer blood transfusions and excellent patient acceptance. However, there are significant effects on training requirements for future urologists, since those operations becoming obsolete form the bulk of open surgery for training.

Meanwhile, many isolated general surgeons are unable to perform the newer endoscopic procedures, causing an increase in overall urological manpower needs.

Personal View on Australasian Urological Training and Manpower

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Structured urological training as a prerequisite for the second part FRACS examination in urology has been established in Australia for a little over a decade. As it is non-existent in the United Kingdom, the American Urology Boards have provided a role model for the establishment of such a programme in Australasia. Our programmes have disadvantages when compared with the more established American training. The Australian Government Hospital system and restrictions on elective surgery, the limited number of staff urologists, limited urological research, lack of paediatric urology as an integrated part of adult urological training, together with the lack of effective urological rotations outside the Government Hospital system, all act to limit training potentials in Australia. These factors are being addressed by the Urology Board.

A major problem for new trainees is the change in urology itself, where all but cancer surgery and some reconstructive surgery is performed either endoscopically or percutaneously. This has 2 effects. Firstly, it limits exposure to open surgery by urological trainees; secondly, at a manpower level it has decreased the amount of urological surgery being performed by non-specialist urologists throughout Australasia. As a consequence there is a need to move the manpower basis from city-based urologists to large provincial centres throughout Australia to provide a more even standard of care throughout the country.

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PAEDIATRIC UROLOGY

Natural History of Pelviureteric Obstruction Detected by Prenatal Sonography

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Summary—Fifty-six infants with prenatally diagnosed hydronephrosis are reported. In all instances the diagnosis was confirmed postnatally and at renography 45 were obstructed; 38 obstructed kidneys (84%) and all of the non-obstructed kidneys had a differential function exceeding 40% of total function.

Latterly we have come to recommend early pyeloplasty only if differential function of a renographically obstructed kidney is less than 40%; 6 early pyeloplasties were performed for this reason; 28 infants (30 renal units) were managed non-operatively and 18 of these (19 renal units) were reassessed renographically. In 11 the obstruction persists. Sonography demonstrated improving hydronephrosis in 8 kidneys with resolution in 5 and no change in 6. Of the other 10 infants (11 renal units), the hydronephrosis has improved in 4, resolved in 1 and remains unchanged in 6.

Our experience suggests that neonatal and early pyeloplasty can be restricted to a modest number of infants in whom there is impaired renal function. In cases with normal function the natural history appears essentially benign and does not justify routine pyeloplasty.

Fetal uropathies occur in 1 in 600 to 800 pregnancies (Smith *et al.*, 1987; Arthur *et al.*, 1989) and are now routinely detected by prenatal sonography. The commonest lesion diagnosed by this means is pelviureteric obstruction (Turnock and Shawis, 1984; Thomas *et al.*, 1985), a condition which, until recently, was encountered mainly in older children and adults presenting with symptoms and, for that reason, surgical correction was almost always advised. Implicit also were assumptions that the function of affected kidneys, judged radiologically, was usually somewhat impaired and that, without treatment, deterioration was inevitable (Chisholm and Osborn, 1976).

Initially our approach to prenatally diagnosed cases was conditioned by these time-honoured beliefs, so that pyeloplasty was routinely performed within a few days of birth. Later this policy mellowed to the extent that surgery was often deferred for up to 3 months and on one occasion during this period complete, spontaneous resolution of hydronephrosis was observed. Perhaps, it was thought, this represented an example of non-obstructive dilatation, so diuresis renography was added to the investigative regime and pyeloplasty recommended only where this confirmed obstruction.

Soon it became appreciated that this same investigation also demonstrated that most affected kidneys appeared to function normally. So when was surgery required in these otherwise healthy infants? Doubts extended beyond the much debated issue of immediate versus delayed pyeloplasty (King *et al.*, 1984; Bernstein *et al.*, 1988; Dejter *et al.*, 1988) to a consideration of whether pyeloplasty was ever routinely advisable for infants with prenatally diagnosed pelviureteric obstruction, a condition of quite unknown natural history. Thus we came to adopt an essentially conservative policy, early results of which follow.

Read at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

Patients and Methods

In the years 1984 to 1988 inclusive, 56 infants (40 male, 16 female) presenting with prenatally diagnosed hydronephrosis were found on investigation to have typical radiological (37 cases) or sonographic (19 cases) appearances of pelviureteric obstruction, including 2 bilaterally and 2 in solitary functioning kidneys.

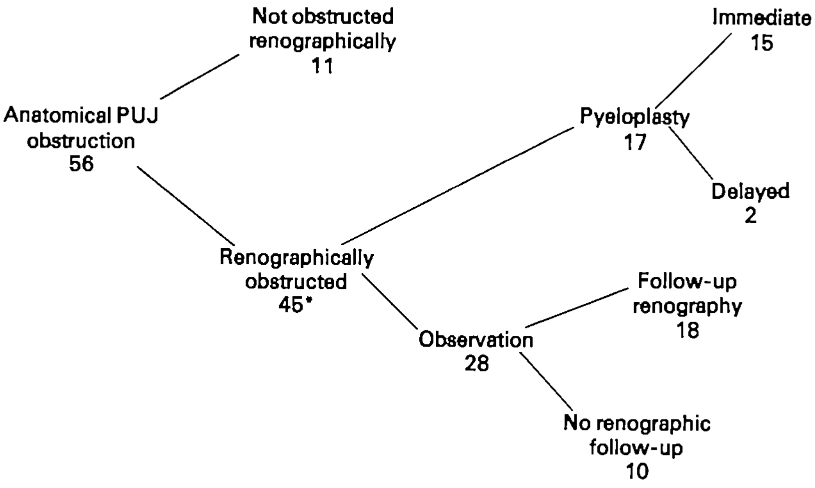
Renographic assessments (^{123}I Hippuran in 30 cases, ^{99}Tc-diethylene-triaminepenta-acetate (DTPA) in 15, ^{99}Tc-mercapto-acetyl-triglycine (MAG 3) in 8 and ^{99}Tc-dimercaptosuccinic acid (DMSA) in 3 cases) were obtained at 1 to 9 months of age (mean 3). Differential renal function was assessed from estimated glomerular filtration rate (^{99}Tc-DTPA), effective renal plasma flow (I^{123} Hippuran, ^{99}Tc-MAG 3) or differential uptake of isotope (^{99}Tc-DMSA); in cases with bilateral disease or a solitary functioning kidney, reference was made to normal age-related values. Renographic obstruction was considered present if, 16 min after frusemide injection, there was no fall in the excretion curve (Type II) or a fall of less than 50% (Type IIIb) (Lupton *et al.*, 1985).

A conservative policy evolved during 1985 and, from 1986 onward, operative intervention was advised only where renographically assessed function of the affected kidney lay below 40% of total. If function was severely impaired, percutaneous nephrostomy was established and pyeloplasty recommended only if a month's such drainage improved function above 20% of total. Other cases, with or without renographic obstruction, were managed expectantly, with sonography repeated at intervals of 3 to 6 months and renography between 1 and 2 years of age dependent upon the degree of hydronephrosis. Delayed pyeloplasty was performed in the event of increasing hydronephrosis on sonography or deteriorating renal function on renography. Cystography was not undertaken, nor did patients receive antibiotic prophylaxis. Growth was monitored at clinic visits when routine urine cultures were also obtained.

Results

At birth, 1 infant had giant hydronephrosis and a palpable lesion; others were without physical signs and in good health. To date no patient has developed symptoms and there has been no documented urinary infection. Growth has been normal except in 1 infant who did undergo pyeloplasty.

General progress of the patients is shown in Figure 1 and findings on initial renographic assessment in Table 1.


Not obstructed renographically 11
Anatomical PUJ obstruction 56
Renographically obstructed 45*
Pyeloplasty 17
Immediate 15
Delayed 2
Observation 28
Follow-up renography 18
No renographic follow-up 10

* Including 3 with DMSA scans.

Fig. 1 Progress of patients.

Table 1 Differential Function of Hydronephrotic Kidneys on Initial Renographic Assessment

Unobstructed	*No.*	*Obstructed*	*No.*
>45%	9	>45%	24*
40–45%	2	40–45%	16
		20–39%	6†
		<20%	1

* Including 1 case evaluated by DMSA scanning.
† Including 2 cases evaluated by DMSA scanning.

Table 2 Change in Function of the Obstructed Kidney from Initial to Follow-up Renography

Improved	2
Unchanged	17
Deteriorated	0

In 11 instances, despite typical anatomical appearances, pelviureteric obstruction was not confirmed by renographic criteria (11 Type IIIa curves (Lupton *et al.*, 1985)). The 2 patients with a solitary functioning kidney come within this group. Follow-up renography at 7 to 38 months of age (mean 24) has been obtained in 6 instances and confirms continuing non-obstruction and unimpaired function. Sonographically, at ages ranging from 12 to 38 months (mean 27), hydronephrosis was unchanged in 2 instances, lessened in 4 and resolved in 5.

In 45 patients pelviureteric obstruction was considered confirmed, by dynamic diuresis renography in 42 cases (44 renal units, 19 Type II curves, 25 Type IIIb curves) and, in 3 having DMSA assessment, by Whitaker test in 1 instance and, by inference, from impaired function in 2. Seventeen infants underwent pyeloplasty (1 following preliminary nephrostomy drainage), all without complication and with an anatomically satisfactory result. Fifteen procedures were performed shortly after the initial renogram, 6 because differential function of the affected kidney lay below 40% and 9, where differential function exceeded 40%, before the conservative regime had become established. Two patients, both with normal differential function, had delayed pyeloplasty, 1 at 8 months, because of increasing hydronephrosis, the other at 16 months when repeat renography although confirming continuing satisfactory function of the affected kidney, showed inexplicable deterioration of the contralateral unit. In only 1 instance did parents report improvement in well-being following pyeloplasty.

Twenty-eight patients (30 renal units) with renographic evidence of obstruction and differential function exceeding 40% of total continue to be managed expectantly. In 18 cases follow-up renography (^{99}Tc-MAG in 12 cases; ^{99}Tc-DTPA in 4 and ^{123}I Hippuran in 2) has been obtained at ages ranging from 10 to 54 months (mean 26) (Table 2). In the 11 patients with persisting renographic obstruction, hydronephrosis, assessed by sonography, has lessened in 5 instances (Fig. 2) and resolved in 2. Among 7 cases where renography indicates resolution of obstruction (including 1 with bilateral disease), hydronephrosis has decreased in 3 cases (Fig. 3) and resolved in another 3.

Ten infants have yet to have renographic reassessment (including 1 with bilateral disease); current ultrasound examinations at 3 to 47 months of age (mean 13) show no change in hydronephrosis in 6 instances, improvement in 4 and resolution in 1.

Discussion

It is widely held, especially within North American circles, that infants with prenatally diagnosed pelviureteric obstruction should routinely undergo pyeloplasty during the neonatal period, proponents of this view contending that the function of affected kidneys is frequently depressed when assessed neonatally by ^{99}Tc-DTPA renography and that if the kidney is "decompressed" by pyeloplasty dramatic recovery may ensue or, if function chances to be good, this can be maintained only by surgical intervention (King *et al.*, 1984; Bernstein *et al.*, 1988; Dejter *et al.*, 1988).

Our findings do not relate exactly to these propositions. Quite deliberately, we did not undertake renography neonatally, when renal function is rapidly adapting from high fetal to low postnatal urinary output. In addition, our functional assessments mainly relate to effective renal plasma flow derived from ^{123}I Hippuran or ^{99}Tc-MAG 3 renograms rather than glomerular filtration rate from ^{99}Tc-DTPA renography. Nonetheless it appears that both methods provide a similar estimate of renal function except in the context, not germane to present purposes, of severe, acute obstruction (Bricker, 1969; Rehling *et al.*, 1988). A possible explanation of the discrepancy between present and North American experience is that the function

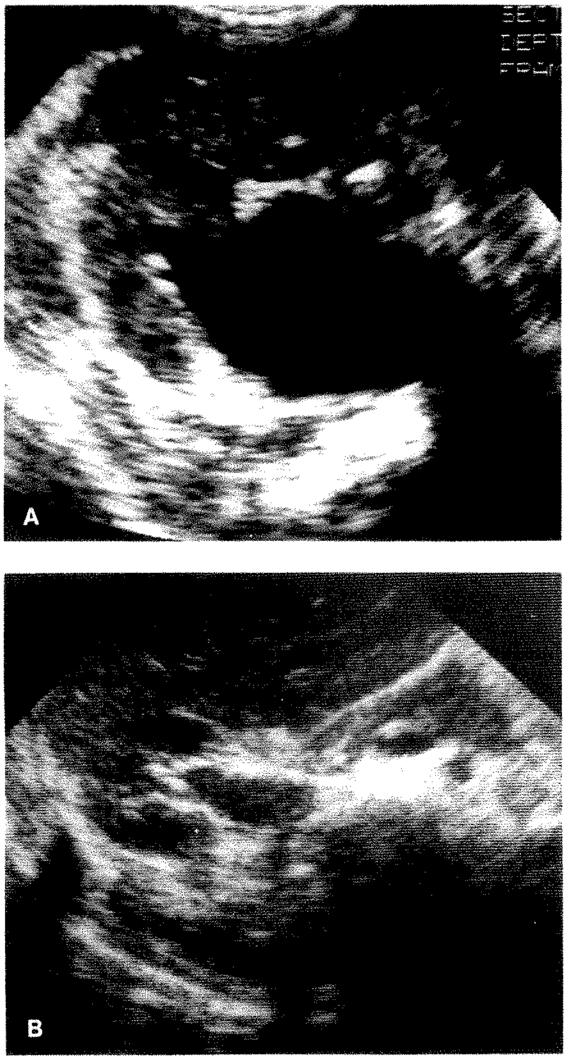


Fig. 2 (A) Infant with giant right hydronephrosis at birth; sonography at 3 months still shows massive pelvic dilatation. (B) Sonography at 3 years of age demonstrates substantial resolution of hydronephrosis.

of kidneys prenatally affected by pelviureteric obstruction improves spontaneously within the first few weeks after birth.

Renal "decompression" by pyeloplasty implies that with pelviureteric obstruction intrapelvic pressure is persistently elevated. Studies addressing this issue have shown that the reverse is generally the case (Johnston, 1969; Poulson *et al.*, 1987). If so, the notion of "decompressive" pyeloplasty is usually fallacious and it is no wonder that renal function is, for the most part, well preserved and remains so.

On the basis of our findings we consider that early pyeloplasty can be restricted to the modest number of infants with unilaterally compromised function of any degree (or bilateral involvement with mild impairment) and neonatal pyeloplasty to the exceptional case with severe bilateral disease (or a solitary functioning kidney) and global renal impairment.

When adopting a conservative approach we had anticipated that in the long term hydronephrosis in the presence of renographically determined obstruction would persist or deteriorate and, in the latter event, renal function also. So far this has not occurred and in an appreciable proportion of cases spontaneous improvement has occurred. Perhaps this is not surprising, bearing in mind that the upper renal tracts of infants have not the physical properties of drainpipes but are living, growing and adaptable tissues, furthermore that the fundamental pathology of pelviureteric obstruction remains unknown and hence is not necessarily irreversible. Whilst the ultimate fate of these kidneys remains to be seen, our data do not lend support to a policy of routine pyeloplasty for prenatally diagnosed cases of pelviureteric obstruction.

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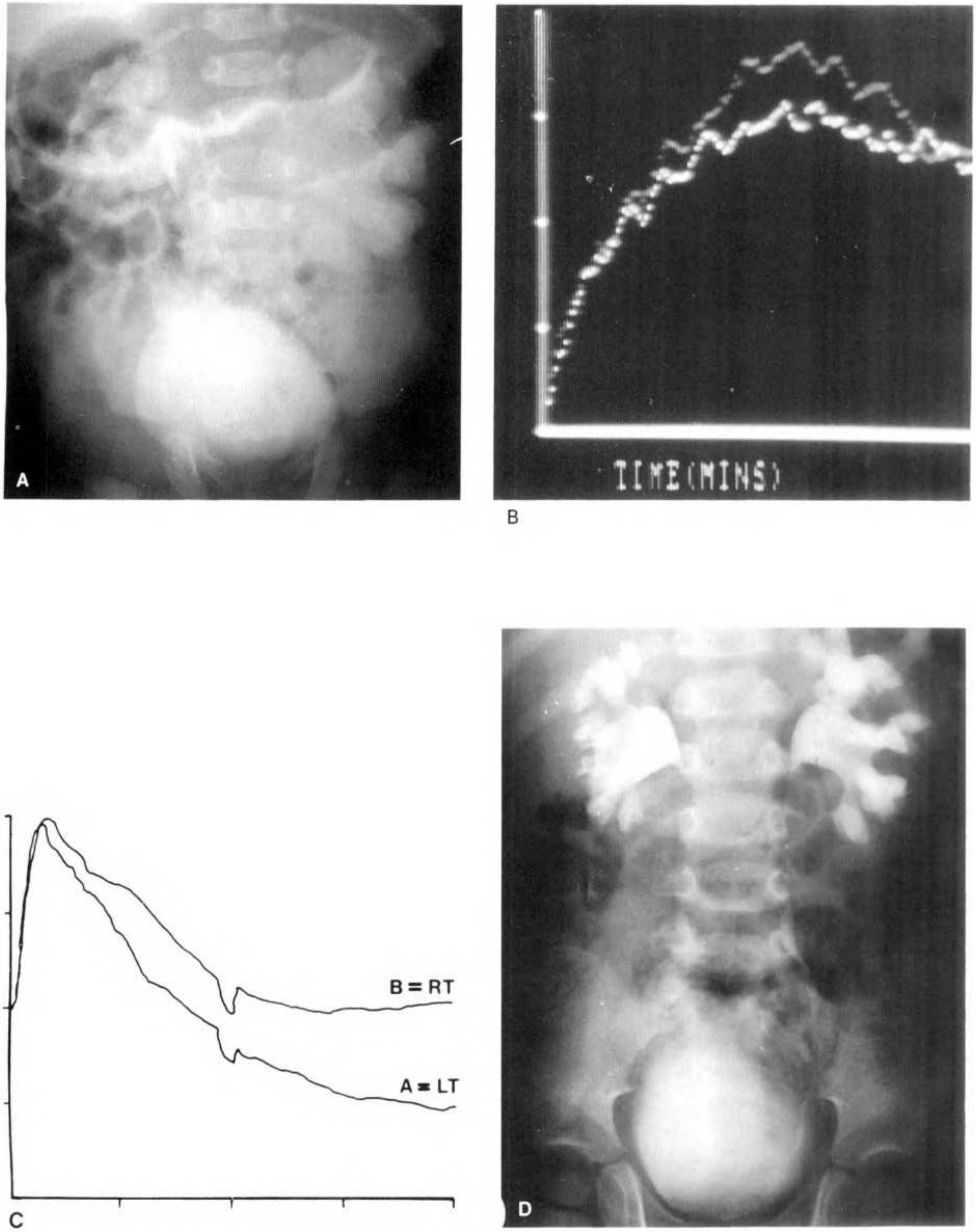

Fig. 3 (A) IVU showing marked bilateral hydronephrosis at 7 weeks of age. (B) Diuresis ^{123}I Hippuran renography at same age with bilaterally obstructed (type II) curves. (C) ^{99}Tc MAG 3 diuresis renography at 3 years of age indicates substantial resolution of obstruction. (D) IVU at 3 years of age showing bilaterally decreased hydronephrosis.

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Buried Penis. A Novel Approach

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Summary—Buried penis is a congenital abnormality in which the phallus is concealed within the subcutaneous tissue. The corporal bodies and glans have developed normally. A deficiency of penile shaft skin in association with abnormal mobility of the skin gives rise to the phenotypic appearance. The skin defect may be related to an abnormal attachment of dartos muscle during embryogenesis. Correction of this condition requires separation of these abnormal muscular attachments and provision of skin coverage of the penile shaft. It is imperative not to circumcise the patient as this will worsen the skin deficiency. We describe a novel technique for correcting buried penis performed on 12 patients at the Great Ormond Street Hospital for Sick Children. A satisfactory cosmetic result was obtained in all patients.

Buried penis is a congenital abnormality in which the phallus is concealed within the subcutaneous tissue (Fig. 1). The buried penis may be partial or complete; in the former, the proximal penile shaft appears as a shortened phallus while in the latter the phallus is invisible as it is concealed below the abdominal wall (Crawford, 1977). It is emphasised that the corporal bodies and glans develop normally. The defect is related to a deficient penile skin which has abnormal mobility over the shaft of the penis.

The basis for surgical correction is directed at separating the abnormal dartos attachments and providing adequate shaft skin coverage with the inner preputial skin. Several procedures, including Z-plasty, skin grafting, preputial unfurling, penile fixation and suction lipectomy, have been described (Crawford, 1977; Johnston, 1977; Devine *et al.*, 1984; Donohoe and Keating, 1986; Maizels *et al.*, 1986). We present a novel technique to correct this condition and present a current review of the literature.

Patients and Methods

Twelve boys with buried penis, aged 8 to 24 months, were evaluated at Great Ormond Street Hospital for Sick Children between 1986 and 1988. Normal corporal bodies and glans were palpable in all cases and no child had any prior urological problem.

Procedure

Patients are placed in the supine position and the foreskin drawn back to expose the penis. If phimosis

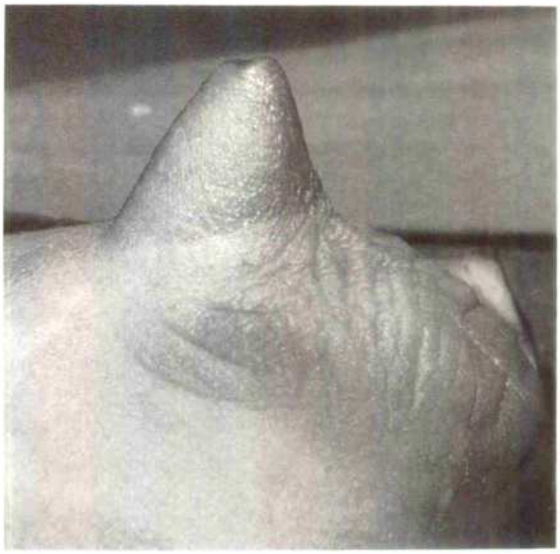

Fig. 1 Buried penis. The phallus, which develops normally, is concealed within the subcutaneous tissue.

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is present, a 0.5 cm ventral incision is made to permit complete retraction of skin over the penis. A circumferential incision is made proximal to the corona and the dorsal penile skin with the preputial skin is dissected free from the penile shaft at the level of Buck's fascia. The dissection is continued proximally to free the abnormal dartos attachments on the ventral aspect of the penis. The ventral skin defect becomes apparent after complete degloving of the penis.

A rectangle of inner preputial skin is incised, the measurements of which should coincide with the amount of deficient ventral skin (Fig. 2). Occasionally, some outer preputial skin must be included in the rectangle as the inner preputial skin may be of inadequate size to cover the ventral skin defect. An island pedicle flap is created by careful dissection of the subcutaneous tissues from the outer preputial and penile skin. This dissection is more difficult proximally at the junction of the outer preputial skin and abdominal wall skin. When an adequate pedicle length has been achieved, a window should be made in the base of the pedicle for buttonhole transposition of the island flap to the ventral aspect (Fig. 3). Thus the inner preputial skin is used to replace absent ventral shaft skin. The flap may be placed on the defect longitudinally or as a complete or incomplete transverse wrap. The flap can be reapproximated to itself on the dorsal aspect of the penis (Fig. 4). The outer preputial skin is used for dorsal or proximal penile shaft coverage. The coronal edge and proximal skin are sutured circumferentially to the preputial flap (Fig. 5). A silicone urethral catheter is inserted *per urethram* and a silastic foam dressing is used for compression.

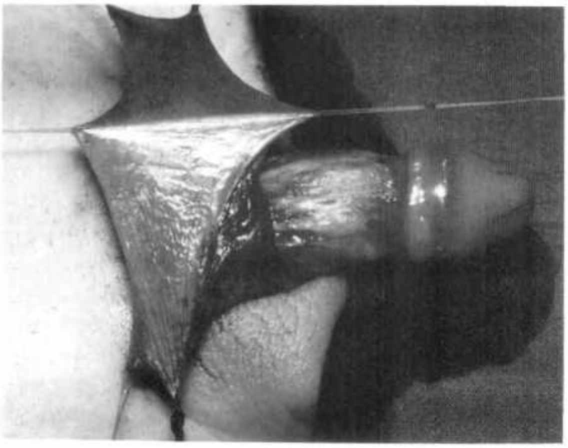

Fig. 2 After degloving the phallus, a rectangle of inner preputial skin is incised; skin flap dimensions coincide with the amount of deficient ventral skin.

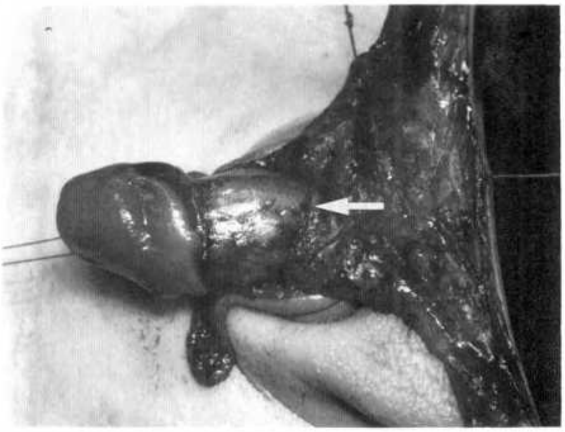

Fig. 3 A window (arrow) is made in the pedicle for buttonhole transposition of the island flap.

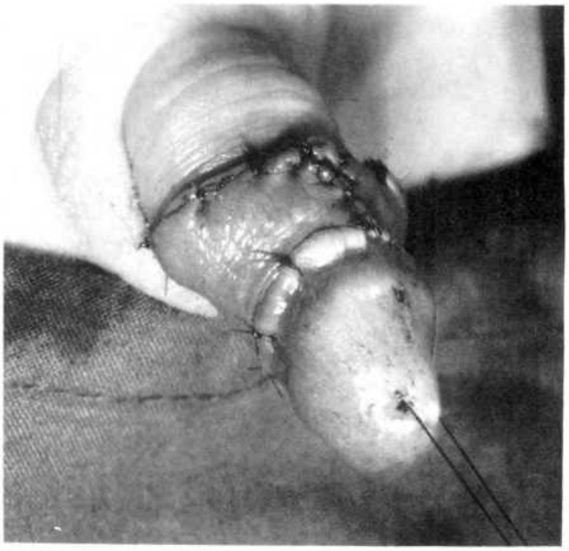

Fig. 4 The inner preputial flap is circumferentially wrapped around the ventral aspect of the penis and reapproximated to itself on the dorsum.

Results

Patients were observed post-operatively and cosmetic results were satisfactory in all cases. No micturition difficulties or abnormalities of erection were evident.

Discussion

The finding of a small or absent phallus usually warrants immediate clinical investigation. The differential diagnosis includes micropenis, penile agenesis, buried penis, concealed penis and webbed

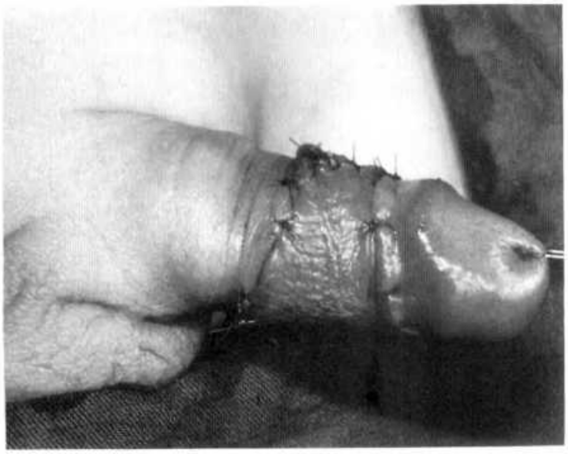

Fig. 5 Completed repair. Deficient penile skin has been replaced with the inner preputial skin.

penis. Micropenis and penile agenesis require urgent chromosomal and endocrinological investigation for proper gender assignment. In the latter 3 conditions, however, normal penile, corporal and glanular development occurs and no further investigations are necessary. Despite normal corporal and glanular development, however, we recommend surgical correction to improve the phenotypic appearance of the phallus.

Buried penis, which may be either partial or complete, is a rare congenital abnormality in which the penile shaft is buried in the subcutaneous tissue. In partial cases, the proximal half of the shaft is buried in the subcutaneous tissue and gives rise to a stumpy-looking penis. In the most severe cases, the penile shaft is totally invisible and the prepuce is continuous with the abdominal wall above and the scrotum below, hiding the phallus completely (Crawford, 1977). The glans and corpora are completely normal in all cases and the major deformity is in skin cover of the organ. The deficiency of shaft skin may not be circumferential but usually occurs on the ventral aspect of the phallus. It appears that this defect in shaft skin coverage is due to abnormal attachments of the dartos muscle to the corporal bodies during penile development. These abnormal fibromuscular attachments cause a tethering on the penile shaft skin to the abdominal wall, thus preventing normal skin development. When these bands are incised surgically at the time of correction, the ventral skin defect and length of the corporal bodies become apparent. Incision of these tethering bands is the initial step in correcting the phenotypic abnormality. The final manoeuvre is to relocate skin in a suitable manner to correct the ventral defect. We used inner preputial skin because it is easily accessible and gives an excellent cosmetic appearance.

Buried penis differs from a concealed penis as the latter condition is a penis concealed behind protruberant suprapubic fat. It often appears in obese children and is treated simply with weight reduction. Induced erections demonstrate no deficiency of penile shaft skin, unlike the deficiency seen in buried penis. Surgical intervention is not often required. Devine *et al.* (1984), however, described a surgical approach for correction. At operation, they demonstrated dysgenetic dorsal bands and removal of this dysgenetic tissue produced good cosmetic results in 20 patients. These dysgenetic dorsal bands may be similar to those which are seen in buried penis; the differences in penile shaft skin in the 2 conditions may be related to the degree of abnormal dartos attachments which occur during embryogenesis.

Webbed penis is a milder condition than either buried or concealed penis. In this disorder, a web of tissue ventrally tethers the phallus to the scrotum (Crawford, 1977). This condition is considered to be a mild form of buried penis as a ventral skin defect does exist. In correcting this condition, the skin web itself may be used to cover the ventral skin defect (Johnston, 1977).

It is important to recognise a child with a buried penis since it is mandatory that circumcision is not performed. This preputial skin is necessary for surgical correction of the penile skin deficiency. Several techniques have been devised to correct the buried penis. Early reports which describe this condition are confusing, since distinctions between buried penis, concealed penis and webbed penis were not made. Crawford (1977) was the first to classify these conditions and he described a technique using S-shaped skin flaps for correction. In addition, he demonstrated tethering bands holding the penis to the abdominal wall and stressed the importance of incising these bands. Residual skin defects were then corrected with medium thickness free skin grafts.

Maizels *et al.* (1986) proposed a revised classification system for the "inconspicuous" penis which helped them to plan surgical therapy. In their new classification, buried penis is divided between young children with poor skin suspension and adolescents with localised adiposity. Other categories include webbed penis, trapped penis after improper circumcision and micropenis. For children with poor suspension, burial occurs because suprapubic fascia fails to anchor the penile skin to the deep fascia; correction is achieved by anchoring skin at the penile base to the pubis. For adolescent adiposity, in addition to anchoring the penis to the pubis, a suction lipectomy is performed. Seven boys of varying ages and with various forms of penile concealment were treated by these varying techniques; good results were achieved in all cases.

To obviate the necessity for free skin grafting, Donohoe and Keating (1986) described a preputial unfurling technique. Their technique requires dissection between the inner preputial lining and outer preputial skin and unfurling the freed layer of foreskin as a preputial sleeve. They demonstrated good cosmetic and functional results in 4 cases.

We have devised a novel technique which corrects buried penis by providing adequate penile shaft skin coverage and removing abnormal dartos muscle attachments. We recommend early surgical correction to improve the cosmetic appearance of the phallus. Critics have advised waiting until puberty when, under the influence of hormonal stimulation, the penis will enlarge adequately. However, we feel it inadvisable to wait until puberty for "nature to take its course" and subject both child and parents to many years of concern. Our good results have strengthened our view that this congenital abnormality should be corrected in early infancy.

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Parameatal Urethral Cysts of the Glans Penis

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Summary—Parameatal urethral cysts are uncommon in the male. We have seen 9 cases and have reviewed these and the 35 cases reported in Japan between 1919 and 1984.

The cysts recurred after rupture or aspiration in 3 cases and complete excision is recommended.

Since Thompson and Lantin (1956) reported 2 cases of parameatal urethral cyst in the male there have been few other reports (Shiraki, 1975; Hill and Ashken, 1977). Ohno (1919) described 5 cases for the first time in Japan. We present a further 9 patients and review 35 cases of parameatal urethral cyst reported in Japan from 1919 to 1984 (Oka *et al.*, 1978; Nakane *et al.*, 1984).

Patients and Methods

The characteristics of the patients are summarised in Table 1. They ranged in age from 9 months to 33 years (average 7.8 years); 7 patients were less than 5 years old and in 3 cases the cyst had been found at birth. In all cases the cyst was located on the glans penis near the meatus. Four patients presented with burning urination and 1 with itching at the parameatus; 8 patients had noticed a parameatal urethral mass before attending hospital.

Histological examination of the cyst showed columnar cell epithelium in 5 cases, transitional cell epithelium in 3 and columnar and cuboidal cell epithelium in 1. Of the 6 patients with columnar cell epithelium, 4 had 1 layer of columnar cells and 2 had stratified columnar cells. Spontaneous rupture of the cyst occurred in 1 case. This patient declined excision and the cyst recurred. Complete excision of the cyst was performed in 8 patients without recurrence or complications.

Discussion

A total or 35 cases of male parameatal urethral cyst have been reported in Japan between 1919 and 1984. Adding our 9 cases to these produced 44 cases for review. The patients ranged in age from 9 months to 43 years (mean 17.7 years); 20 (45.5%) were less than 15 years old. An asymptomatic mass was present in 75% (Fig. 1). Burning urination, irregular urinary stream or itching at the urethral meatus were present in 25%.

The aetiology of these cysts is unclear. Thompson and Lantin (1956) stated that parameatal urethral cysts occurred in the process of delamination or separation of the foreskin from the glans, while Shiraki (1975) believed that occlusion of a paraurethral duct was the cause. Parameatal urethral cysts

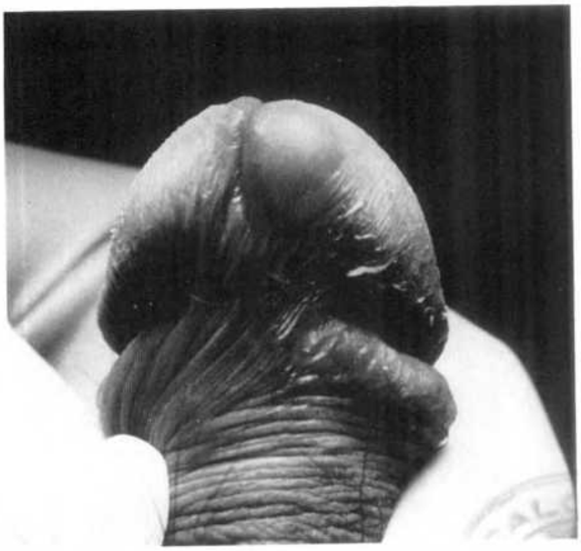

Fig. 1 Parameatal urethral cyst in Case 8 (15-year-old boy).

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Table 1 Characteristics of Patients

Patient no.	*Age (years)*	*History*	*Treatment*	*Histology*
1	1	Parameatal cyst noticed soon after birth	Excision	Stratified columnar
2	5	Itching at glans present for several months	Excision	Transitional
3	33	Swelling of parameatus present for 15 years; swelling increasing in size	Rupture	—
4	5	Mother noticed parameatal cyst 1 year previously; recent development of burning urination	Excision	Columnar
5	3	Parameatal cyst noticed soon after birth; recent development of burning urination	Excision	Stratified columnar cuboidal
6	9 months	Parameatal cyst noticed at examination of mass	Excision	Columnar
7	3	Swelling of parameatus present for 3 months; recent development of burning urination	Excision	Columnar
8	15	Burning urination present for several months	Excision	Columnar
9	3	Asymptomatic parameatal cyst present for 3 years	Excision	Transitional

were noticed at birth in 6 of 44 patients and a congenital aetiology is most likely in these cases (Thompson and Lantin, 1956). A 32-year-old patient had an infected cyst (Nakane *et al.*, 1984). This may represent an acquired cyst due to occlusion of the paraurethral duct following infection or trauma.

Table 2 Histology of Parameatal Urethral Cyst

Histology of epithelium	*No. of patients*
Columnar	17
Transitional	7
Columnar and cuboidal	4
Squamous	2
Columnar and squamous	2
Columnar and transitional	2
Unknown	10
total	44

Histological examination of the cyst wall epithelium showed columnar (Fig. 2), transitional (Fig. 3) and cuboidal and squamous cell epithelium (Table 2). Columnar cell was the most common and these epithelia are seen as normal urethral mucosa. Thompson and Lantin (1956) suggested that cuboidal cell epithelium might be of endodermal origin. Cole and Helwig (1976) stated that the cells lining the cyst contained a variable amount of periodic acid Schiff-positive material found in the cytoplasm on the luminal side of the cells.

The cysts recurred after rupture or aspiration in

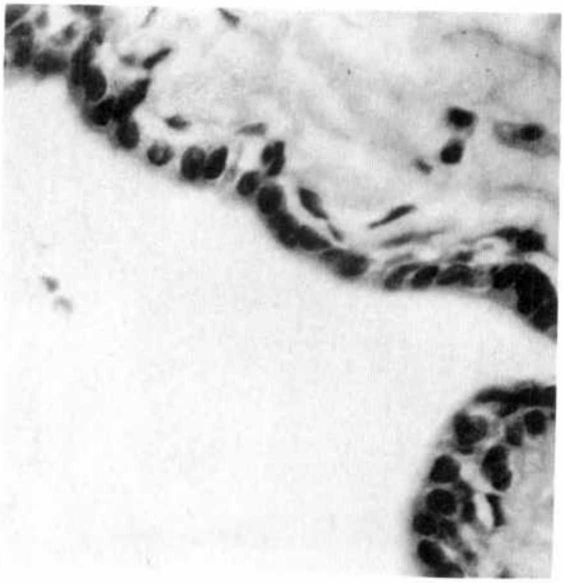

Fig. 2 Columnar cell epithelium lining a urethral cyst.

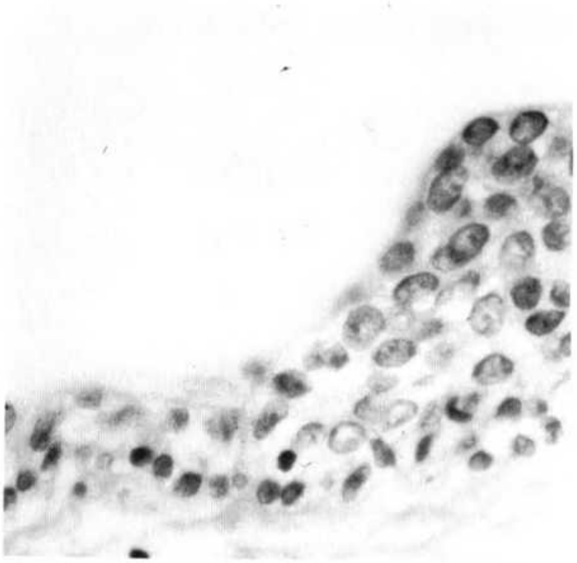

Fig. 3 Transitional cell epithelium lining a urethral cyst.

3 patients and complete excision is therefore recommended.

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Case Reports

Wegener's Granulomatosis Presenting as Granulomatous Prostatitis Causing Urinary Retention

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Case Report

A 51-year-old man was admitted with a short history of increasing difficulty in voiding, culminating in acute urinary retention. His renal function was normal. He had no proteinuria. Urine contained 30 red cells and 150 white cells per mm^3 but no significant infection. He had no symptoms of respiratory disease. His prostate gland was moderately enlarged. Endoscopic appearances were those of a necrotic prostate malignancy. Histology from transurethral resection of prostate revealed severe necrotising granulomatous prostatitis (Fig.). Following a prompt recovery he was readmitted 6 weeks later with weight loss, arthralgia, rhinorrhoea, cough with haemoptysis and extensive ulceration of nose and nasopharynx. Bronchoscopy showed extensive bilateral infiltration of the bronchial tree. Bronchial and nasal biopsies revealed an inflammatory reaction with multinucleate giant cells highly suggestive of Wegener's granulomatosis. No evidence of malignancy or tuberculosis was found. Neutrophil cytoplasmic antibody was positive.

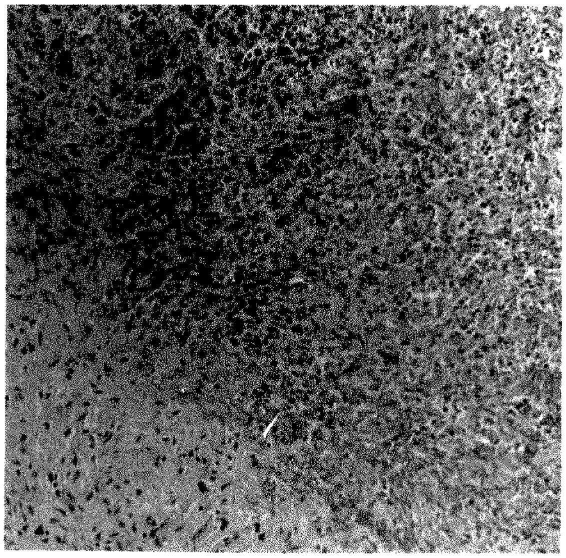

Fig. Large areas of necrosis are present within the prostate. (H and E ×200).

Comment

Several specific and non-specific causes of granulomatous prostatitis have been described (Epstein and Hutchins, 1984), but the presentation of our patient in urinary retention with Wegener's granulomatosis in the absence of respiratory involvement appears to be unique. The pathogenesis of Wegener's granulomatosis is unresolved. Attempts have been made to implicate bacterial and fungal agents and the finding of antibodies to neutrophil cytoplasmic antibodies suggests an autoimmune aetiology (Van der Woude *et al.*, 1985). The presentation in this patient suggests that the portal of entry may on occasions be other than the respiratory tract. Wegener's granulomatosis should be considered in the differential diagnosis of granulomatous prostatitis and when necrotising granulomatous lesions present elsewhere (British Medical Journal, 1971).

Acknowledgement

We thank Dr A. H. Burdge for his help in reproducing the photomicrograph.

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Metastatic Renal Carcinoma Mimicking Carotid Artery Aneurysm

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Arteriovenous shunting within malignant tumours is very rare, but it occurs most often within renal carcinomas. We present a case of metastatic renal carcinoma in cervical lymph nodes mimicking a carotid artery aneurysm.

Case Report

An 80-year-old woman presented with 2 soft pulsatile swellings on the right side of the neck posterior to the angle of the jaw; 14 years previously she had undergone radical nephrectomy for clear cell carcinoma of the left kidney. No caval invasion or distant metastases were noted at the time of operation or subsequently detected. Four years prior to presentation a right superficial parotidectomy for a tumour of the lower pole of the parotid had been performed. The histopathological report stated that it was a monomorphic adenoma.

A carotid angiogram (Fig.) was reported as showing "Two large aneurysm sacs . . . possibly communicating with each other . . . and with early venous filling." They did not appear to arise from the internal carotid artery but appeared to be related to a posterior branch of the external carotid artery.

At operation both lesions appeared to be supplied by the occipital artery, but with rapid retrograde filling. The excised lesions were spongy in nature with the appearances of recurrent tumour and on histological examination consisted of "richly vascular" metastatic renal carcinoma within intraparotid lymph nodes. The histology of the previous parotidectomy specimen was reviewed and showed the parotid tumour to be composed of the same cell type as the neck lesion.

Her post-operative recovery was uneventful. She received post-operative radiotherapy to the site of the lesions and at follow-up 30 months later remained well with no evidence of recurrence of her renal carcinoma.

Comment

Arteriovenous (AV) shunting within renal carcinomas is a variable phenomenon even in patients with multiple lesions (Caplan, 1961). Some lesions may show AV shunting whilst others may not. Metastases with a significant AV communication have so far been observed only in bone (Howlett and Caranasos, 1970), despite osseous metastases accounting for only one-third of all metastatic renal carcinoma. On occasion these have been noted to produce pulsatile bone masses (Zucker and Levine, 1958; Vetto *et al.*, 1966).

The delayed appearance of renal carcinoma metastases (as in this case) is well recognised (Kradjian and Bennington, 1965). A prolonged interval between primary excision of a renal carcinoma and the appearance of a suspected AV shunt should not lead one to discount a metastasis from the renal carcinoma as the cause of the shunt.

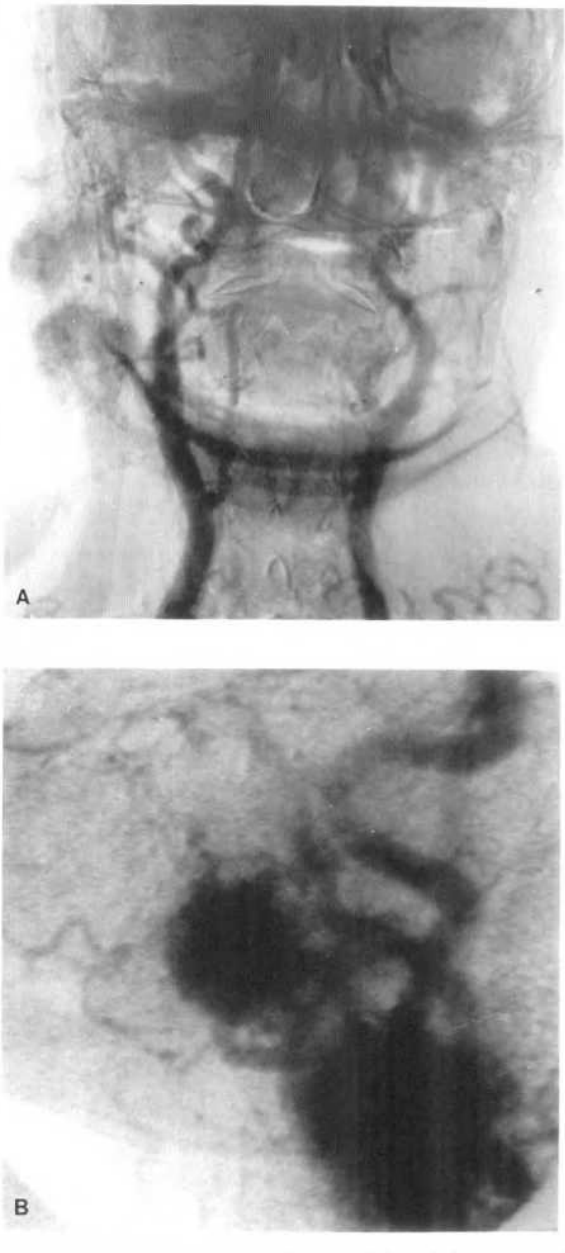

Fig. (A) DSA of carotid arteries. (B) DSA of right external carotid artery.

The mode of presentation of a shunt depends principally upon 2 factors: the degree of microscopic AV communications and the size of the lesion. If the magnitude of shunting is great enough it can produce circulatory effects such as high-output cardiac failure, reversal of which has been recorded following excision of the lesion (Vetto *et al.*, 1966).

If the lesion is small and superficial, but of a highly vascular nature, it may merely present as a pulsatile mass and be mistaken for an aneurysm (as in this case).

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Hamartoma of the Urinary Bladder in an Infant with Beckwith-Wiedemann Syndrome

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Case Report

At birth, this male infant was noted to have macroglossia and hemihypertrophy, two features of the Beckwith-Wiedemann syndrome (Beckwith, 1969). Because of an association of this syndrome with congenital anomalies of the urinary tract, plus a susceptibility to Wilms' tumour and rhabdomyosarcoma (Sotelo-Avila and Gooch, 1976), sonography of the urinary tracts was undertaken at birth and at 3 and 6 months of age. These examinations were normal. At the age of 8 months there occurred terminal haematuria and further ultrasound examination showed a 3 × 0.7 cm tumour within the bladder. Urine analysis was unremarkable. The tumour, arising from the posterior wall of the bladder immediately above the trigone, was resected endoscopically at its base, but, being too bulky to extract *per urethram*, was removed via a small cystotomy (Fig.). Cystoscopies carried out 3, 6 and 18 months post-operatively showed no recurrence.

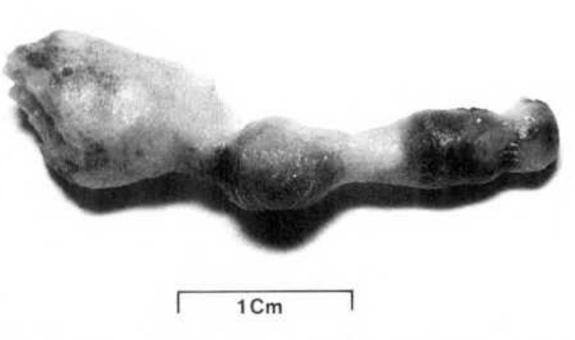

Fig. Macroscopic appearances of the resected bladder tumour: the base lies toward the left.

Microscopically, the polyp had a central fibrous core containing adipose tissue, arterioles and young fibroblasts. Towards the tip there were bundles of smooth muscle cells. Beneath a surface of normal transitional epithelium lay a loose myxoid background plentifully populated with stellate and multinucleate giant cells. There were a few areas of focal ulceration of the mucosa with an underlying mixed inflammatory infiltrate.

Comment

Benign, non-transitional cell tumours of the bladder are rare at all ages and especially so in infants. Patients with Beckwith-Wiedemann syndrome have increased susceptibility to a variety of benign and malignant tumours. No benign bladder tumour has been recorded, but 1 patient who was dying of Wilms' tumour was found at autopsy to have a hamartomatous polyp in the interventricular septum of the heart (Reddy *et al.*, 1972).

In this case, rhabdomyosarcoma was excluded histologically.

Because all elements of the wall of the urinary bladder were present within this benign tumour, it is probably best described as a hamartoma. Alternative histological diagnoses considered were inflammatory pseudotumour (Nochomovitz and Orenstein, 1985) and pseudosarcomatous fibromyxoid tumour (Ro *et al.*, 1986). Both are probably visceral examples of nodular fasciitis, or some other type of benign reactive process, and contain neither adipose tissue nor smooth muscle.

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Venous Infarction of the Testis Secondary to Acute Epididymitis

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Case Report

A 31-year-old man presented with a week's history of a painful left-sided scrotal swelling. There was no history of trauma. Examination revealed a tender, diffuse, non-fluctuant scrotal swelling. Acute epididymo-orchitis was diagnosed and antibiotics prescribed.

Three weeks later there was still a tender swelling in the scrotum. An ultrasound scan showed normal-looking testicular tissue closely applied to an echodense area presumed to be a partially atrophic testis. No abscess or hydrocele was seen. The left testis was explored through an inguinal incision. There was no hydrocele and the testis was enlarged, soft and fluctuant. On incision, it was found to be almost replaced by a haematocele. Orchiectomy was performed.

Microscopy showed total necrosis of the testis and epididymis with extensive haemorrhage and numerous dilated veins within the epididymis, some containing thrombus. The appearances were consistent with venous infarction following obstruction and thrombosis of the pampiniform plexus.

Comment

Testicular infarction following epididymitis is rare and its pathogenesis obscure. Its true incidence is unknown as it may be attributed erroneously to torsion. Necrosis may be secondary to thrombosis of the spermatic artery as reported by Gartman (1961). It may, however, occur with the spermatic vessels remaining patent (Kirk *et al.*, 1982) and 2 possible mechanisms have been postulated; either arterial compression by a tense hydrocele, or venous obstruction and thrombosis. The latter seems more likely as the veins draining the testis converge on the mediastinum testis (Harrison and Barclay, 1948) and so are closely related to the inflamed epididymis.

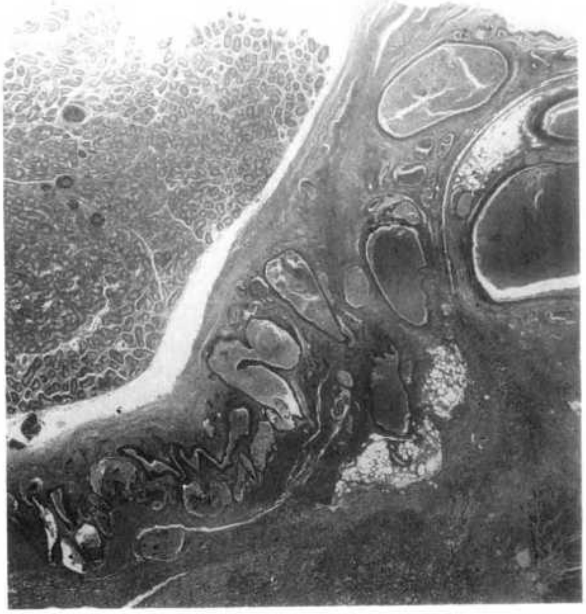

Fig. 1 Section of testis showing necrotic seminiferous tubules (left) and dilated thrombosed vessels (right). (H and E × 10).

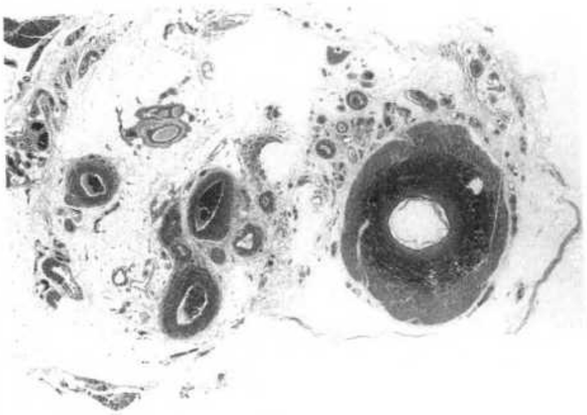

Fig. 2 Section of spermatic cord with the vas deferens (right) and normal vessels (centre). (H and E × 12).

The case we report illustrates a sequence of events previously postulated but not reported. There was no hydrocele and venous thrombosis had occurred. The pathogenesis of the testicular infarction was venous obstruction with secondary thrombosis.

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Wegener's Granulomatosis in the Bladder

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Wegener's granulomatosis is a clinicopathological entity characterised by necrotising granulomatous vasculitis, usually affecting the upper respiratory tract (74%), the lungs (70%) and kidneys (46%) (DeRemee *et al.*, 1976). It affects men and women equally and occurs most commonly in the sixth decade. However, except for involvement of the trigone in connection with Wegener's granulomatosis in the prostate gland (Stillwell *et al.*, 1987), isolated granulomas of the bladder wall have not been reported previously.

Case Report

An 85-year-old woman was admitted with recurrent cystitis and gross haematuria. Intravenous urography revealed a space-occupying lesion in the right lateral part of the bladder. At cystoscopy areas with pronounced necrosis overlying tumour-like lesions were seen on the right side of the bladder wall. Transurethral resection was performed. Biopsies showed tissue with necrotising granulomas and vasculitis, typical of Wegener's granulomatosis (Figs 1 and 2). At cystoscopy 3 months later, no recurrences were seen and the patient was without symptoms.

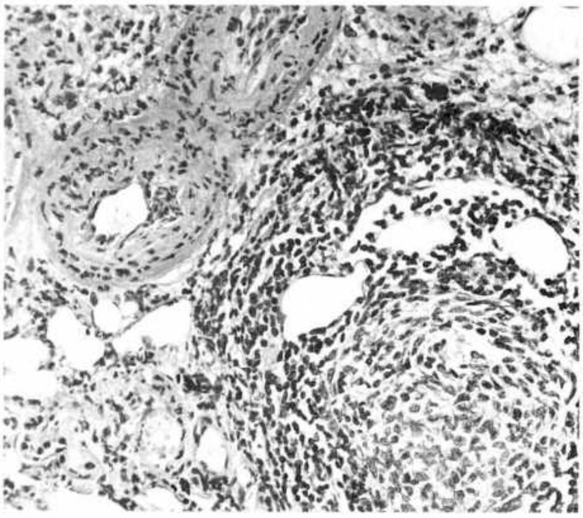

Fig. 1 Bladder biopsy showing vasculitis in an artery and a granuloma typical of Wegener's granulomatosis. (H and E × 250).

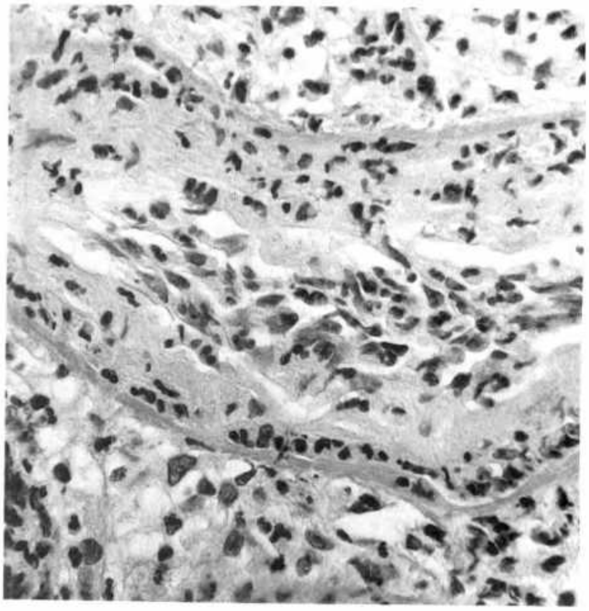

Fig. 2 Bladder biopsy showing arterial vasculitis. (H and E × 400).

In our patient the diagnosis of Wegener's granulomatosis had been made 7 years previously on the basis of para-nasal sinus disease showing the characteristic histology. Chest X-ray at that time revealed several rounded densities in the lungs. Medical treatment with daily cyclophosphamide and prednisone on alternate days was instituted. Complete remission was achieved and after 4 years medical therapy was discontinued. At follow-up 1 year later, no evidence of recurrence was found and the patient remained symptom-free until the bladder became involved.

Comment

Involvement of the urinary tract in Wegener's granulomatosis is usually localised to the kidneys (46%) and renal failure is the most common cause of death among these patients. Other involvements of the genitourinary tract have been reported, though rarely. Prostatic involvement has been reported in 2.3 to 7.4% of patients with Wegener's granulomatosis (Stillwell *et al.*, 1987). However, only 1 case of urinary bladder involvement in a 27-year-old man has been reported earlier, not as an isolated lesion, but as a part of multiorganic Wegener's granulomatosis including the prostate gland (Fienberg, 1953). In the present case the main symptoms were cystitis and gross haematuria. In patients with symptoms of urinary tract infection and previously diagnosed Wegener's granulomatosis in the upper or lower respiratory tract, the possibility of bladder involvement must be kept in mind and cystoscopy is recommended. Once the diagnosis has been verified, treatment with cyclophosphamide daily and prednisone on alternate days is very effective.

It has been suggested that Wegener's granulomatosis is initiated by autoantibody mediated activation of neutrophils, and a significant correlation between disease activity and the serum level of anticytoplasmic antibodies (ACPA) has been found (Van der Woude *et al.*, 1985). Medical treatment was not instituted in the present case because of the negative ACPA test.

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Renal Malignant Fibrous Histiocytoma

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Renal sarcomas are uncommon and constitute only 1 to 3% of all malignant renal tumours. Primary malignant fibrous histiocytoma (MFH) is an unusual type of renal sarcoma. A total of 13 cases have been reported in the English literature and only 9 of these have been fully documented. Due to the rarity of this tumour its treatment has to be based on the behaviour and treatment of MFH in other sites. We report a further case of this tumour and review the literature.

Case report

A 67-year-old woman presented with a 3-month history of right loin pain with associated episodes of urinary frequency and dysuria. She had also noticed a "lump" in her right groin. She had had a cholecystectomy in 1972. Examination confirmed the presence of a mass in the right renal area. Investigations showed normal haemoglobin, blood chemistry and liver function. The chest X-ray was also normal. Urine culture showed a significant growth of *Escherichia coli* which was treated with the appropriate antibiotic. Intravenous urography revealed a mass in the lower pole of the right kidney with a normal left kidney. Ultrasound examination confirmed the presence of a lower pole mass on the right side which had a mixed echo pattern consistent with a renal tumour. At operation a transabdominal approach was made and the lower pole tumour located. A significant degree of perinephric inflammation was noted in association with the tumour. A right nephrectomy was performed and she made an uneventful post-operative recovery. Post-operative radiotherapy was given to the renal bed. The patient was alive, with no evidence of recurrence or metastatic disease 1 year later.

Pathological findings

The operative specimen, which included substantial perinephric fat and a segment of ureter 8 cm long, measured 18 cm from pole to pole and weighed 734 g. Occupying the lower two-thirds of the kidney was an apparently well circumscribed tumour mass, 11 × 9.5 × 8.5 cm. The cut surface was soft, gelatinous and grey in colour, with focal yellowish areas. The tumour appeared to extend very close to, but not through, the capsule.

Microscopic examination showed the tumour to be comprised of spindle cells displaying a patchy storiform pattern, considerable pleomorphism, and foci of necrosis and hyalinisation. Occasional multinucleate giant cells

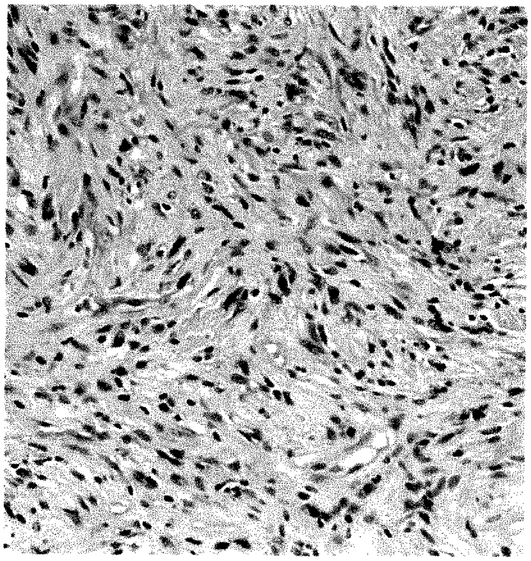

Fig. Spindle cell tumour showing a storiform pattern, nuclear pleomorphism and occasional multinucleate cells. (H and E × 150).

were seen and the mitotic count was 5–7 per 10 high power fields (Fig.). Contrary to the macroscopic impression, tumour cells penetrated the capsule into the perinephric fat.

Immunocytochemistry showed positive staining of the tumour cells for vimentin and α_1-antitrypsin and negative reactions for cytokeratin, S-100 protein and desmin.

The histological and the immunocytochemical features were those of a malignant fibrous histiocytoma.

Comment

Malignant fibrous histiocytoma is one of the commoner types of soft tissue sarcoma (Kearney *et al.*, 1980). It was first described in 1964 by O'Brien and Stout but the pathological classification of these tumours remains difficult and the histiogenesis is still controversial. The newer immunohistochemical techniques have shown markers characteristic of both mesenchymal cells and cells of the mononuclear phagocyte system (Roholl *et al.*, 1985; Strauchen and Dimitriu-Bona, 1986).

Whatever its histiogenesis, MFH behaves as a sarcoma rather than, as its name might suggest, a lymphoma. It has even been suggested that the name be changed to fibrohistiocytic sarcoma in order to reflect this behaviour (Ghandur-Mnaymneh, 1987). In general terms, retroperitoneal MFH accounts for 10 to 15% of all cases of MFH and has a poor prognosis, with a reported 5-year survival rate of only 14% (Kearney *et al.*, 1980) and local recurrence rates of 41% (Kearney *et al.*, 1980) and 44% (Weiss and Enzinger, 1978). Standard treatment is wide local excision. Adjuvant therapy has given disappointing results with only 27 to 48% response rates for combination chemotherapy regimes in advanced soft tissue sarcomas (Karakousis *et al.*, 1982; Brenner *et al.*, 1983; Clamon *et al.*, 1983). Metastatic sarcoma response rates of 14 to 60% are similar (Greenall *et al.*, 1986). The poor prognosis has been correlated empirically with old age, size of tumour, retroperitoneal location, tumour necrosis, distinct storiform pattern and infiltrative growth (Gabbert *et al.*, 1981). Of the 10 fully documented cases of renal MFH, 50% were dead within 1 year (Table). Local recurrence is common (MacEachern *et al.*, 1981) and 20% of the fully

Table Fully Reported Cases

Reference	*Age (years)*	*Sex*	*Side*	*Symptoms and signs*	*Treatment*	*Outcome*
Klugo *et al.* (1974)	62	M	Lt	Pain, mass	Nephrectomy, radiotherapy, chemotherapy	Dead 3/12 (metastatic disease)
Osamura *et al.* (1978)	35	F	Rt	Pain, mass	Nephrectomy	Alive 6/12
Chen (1979)	52	M	Rt	Wt loss, mass, fever	Nephrectomy	Alive 9 years
Raghaviah *et al.* (1980)	33	F	Lt	Pain	Nephrectomy	Dead 9½/12 (local recurrence and metastatic disease)
Chatelanat (1981)	82	F	Rt	Pain, wt loss, mass	Nephrectomy	Dead 2½/12
MacEachern *et al.* (1981)	69	M	Lt	Pain, mass, wt loss	Nephrectomy	Alive 3/12
Singh *et al.* (1982)	68	M	Rt	Wt loss, mass	Nephrectomy	Dead 5/12 (local recurrence)
Chen (1984)	54	M	Rt	Pain, mass	Nephrectomy	Alive 4 years
Ojeda *et al.* (1984)	48	F	Lt	Pain, mass	Radical nephrectomy, chemotherapy	Dead 9/12 (metastatic disease)
McClinton *et al.* (present study)	67	F	Rt	Pain, mass	Nephrectomy, radiotherapy	Alive 12/12

documented cases had local recurrence; it was also noted that 30% of these patients had metastatic disease. In contrast, there are 2 reported cases of longer term survivors (Chen, 1979, 1984) and 4 further cases have been reported but not fully documented (Bennington and Beckworth, 1975; Chatelanat, 1981; Gabbert *et al.*, 1981; Srivinas *et al.*, 1984).

The patients ranged in age from 33 to 82 years (mean 56), with no predominance of either side of disease or sex. The commonest presenting symptoms were loin pain and weight loss. Haematuria was not reported as a presenting symptom, which is in contrast to renal carcinoma where it is a presenting symptom in 62% (Riches, 1963). On examination a loin mass was palpable in 90% of the fully reported cases, perhaps reflecting the aggressive nature of these tumours.

Treatment in most cases was by radical nephrectomy. Adjuvant radiotherapy and/or chemotherapy was used in 3 cases and did not seem to alter the course of the disease.

More documented reports of this type of renal tumour are needed to establish any significant differences that may exist between the natural history of primary renal and retroperitoneal MFH. The prognosis for both groups appears to be very poor.

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Pyelocaliceal Diverticula and Rupture of the Kidney

S. COSTAS and P. J. P. VAN BLERK, *Division of Urology, Department of Surgery, University of the Witwatersrand, Johannesburg, South Africa*

The pathology and clinical problems related to pyelocaliceal diverticula have been reviewed by Wulfson (1980). We report 2 cases in which the presence of the diverticulum led to rupture of the kidney.

Case Reports

Case 1. A 52-year-old male was first seen in November 1980 during his ninth episode of left ureteric colic in 35 years. The stones had always passed spontaneously. Previous investigations, including arteriography, had shown a cystic lesion in the left kidney. For the past year he had been on anticoagulants for a deep vein thrombosis. He was a large muscular man, blood pressure 190/100, with brawny oedema of the left calf. His P.I. was 48% and an abdominal X-ray did not shown any obvious stones. He declined further investigation or treatment but because of haematuria his anticoagulant therapy was reduced. Four days later he passed a small stone. An intravenous urogram showed a caliceal diverticulum about 2 × 1.5 cm arising from the medial side of the neck of the upper major calix of the left kidney with only a few millimetres of renal cortex between it and the renal capsule (Fig. 1). There was a bulge about 5 cm in length on the lateral surface of the kidney with displacement of the middle and lower calices.

Six months later he was admitted with intolerable left loin pain and haematuria containing large blood clots. His B.P. was 80/50 and there was a tender mass filling the whole of the left loin. A diagnosis of spontaneous rupture of the kidney was made. An intravenous urogram

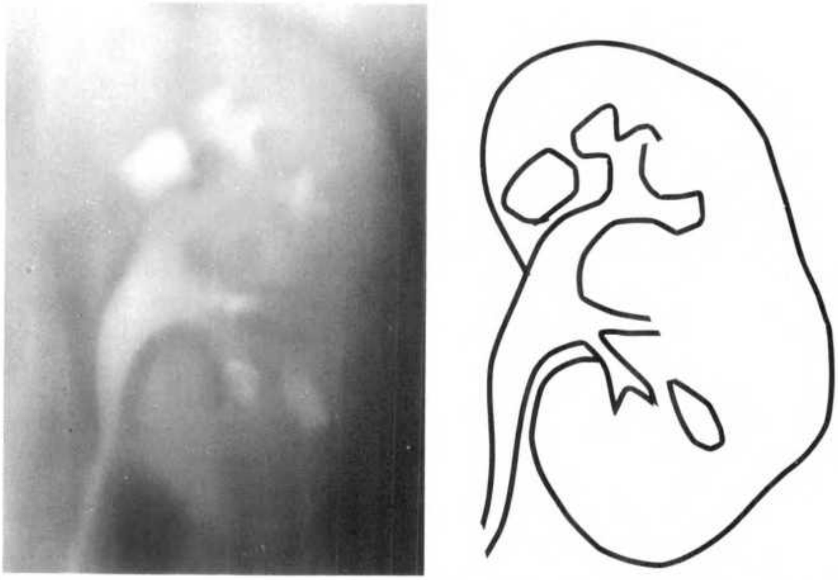

Fig. 1 Intravenous urogram showing caliceal diverticulum medial to upper calix and a space-occupying lesion between the middle and lower calices.

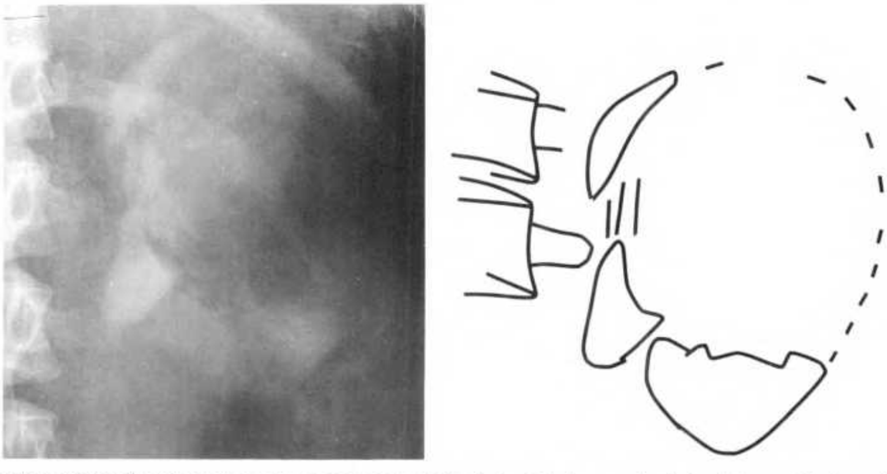

Fig. 2 Intravenous urogram showing a large space-occupying lesion lateral to the renal pelvis with opacified renal tissue displaced supramedially and inferiorly.

showed on the left side a thin nephrogram of cortex above and below the renal pelvis with a large space-occupying lesion obscuring the rest of the renal anatomy (Fig. 2). His Hb was 12.2 g/dl, P.I. was 40% and blood urea was 10.6 mmol/l. He was resuscitated and given 10 mg vitamin K1 and the next day his P.I. was 78% and Hb was 9.7 g/dl. His general condition had remained stable and because of severe pain the kidney was explored. The perirenal space was entered, blood-clot evacuated and lacerations of the cortex were noted on the lateral and supramedial aspects of the kidney. Nephrectomy was carried out. Histology showed that both lacerations had occurred into cavities lined by transitional epithelium. He has not passed stones since then and has recently had a prostatectomy.

Case 2. A 29-year-old male presented with left loin pain. He was overweight and obviously in severe pain. When asked to sit up he became faint, developed a tachycardia of 120/min and a systolic blood pressure of only 80. There was a tender ill-defined mass in the left loin. Intravenous fluids were commenced and a diagnosis of spontaneous rupture of the kidney was made. An intravenous urogram showed a normal right system. On the left there was a large renal shadow but only a nephrogram was obtained which seemed medially displaced and compressed by a large lucent area. At operation a large perirenal haematoma was evacuated and the kidney was found to contain a large, almost central cyst which extended into the lower pole. On the dome of this cyst there was a 2-cm hole where the rupture had occurred. Histology of the cavity showed compressed connective tissue, some chronic inflammatory cells and mild oedema. There was no epithelial lining.

Comment

The repeated stone episodes experienced by the first patient were probably related to the caliceal diverticulum in the upper pole of the kidney. The last episode of ureteric calculus obstruction had probably resulted in back pressure of a sufficient degree to lacerate the caliceal diverticulum. This was complicated by bleeding from anticoagulant therapy which added to the obstruction. A second diverticulum in the lateral aspect of the kidney had on previous intravenous urograms not filled with contrast and appeared to be a simple cyst, but with ureteric obstruction the communication was re-established and the thin cortex overlying this diverticulum had also ruptured. In the second patient, histological proof of a caliceal diverticulum was not convincing but very indicative.

Spontaneous rupture of a pyelocaliceal diverticulum has only been reported once before and occurred during intravenous urography.

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"The Disappearing Catheter"—a Complication of Intermittent Self-catheterisation

J. D. T. MORGAN and P. M. T. WESTON, *Department of Urology, Royal Infirmary, Cardiff*

Intermittent self-catheterisation is an effective way of managing the neuropathic or atonic bladder in both children and adults (Hunt *et al.*, 1984). Whilst considered safe, the procedure has a recognised morbidity rate. Maynard and Diokno (1982) reported nephrolithiasis (11%), cystolithiasis (11%) and epididymitis (14%) in 28 spinal injury patients followed up for a mean of 3.7 years.

We present 2 cases of over-advancement and subsequent loss of the catheter.

Case Report

A 74-year-old female had advanced a catheter into her bladder and was unable to retrieve it. She had been diagnosed as having chronic retention with overflow incontinence and recurrent urinary infections and had performed self-catheterisation 4 times daily for 4 months using a 14 F Nelaton catheter. Prior to catheterisation, she had cut the funnelled connector from the catheter, although the exact reason for this was unclear.

Examination was unremarkable and the catheter could not be visualised at the meatus.

The catheter was removed cystoscopically under local anaesthesia.

Case 2. A 42-year-old female was unable to retrieve a catheter following a vasovagal attack during catheterisation. She had been diagnosed as having an adynamic bladder following abdominal hysterectomy in 1985 and had undergone 2 urethrotomies. Subsequently, she had been performing self-catheterisation 5 times daily for 8 months with a Scott catheter.

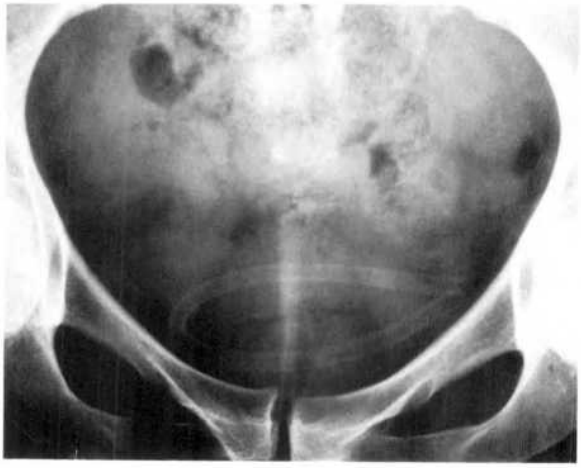

Fig. Plain radiograph of pelvis showing urinary catheter coiled in bladder.

Examination was unremarkable and plain radiography demonstrated the catheter coiled within the bladder (Fig.). This was removed cystoscopically under local anaesthesia.

There were no complications and both patients were discharged home to continue self-catheterisation.

Comment

Instruction in teaching intermittent self-catheterisation has included the development of comprehensive nursing packages (Barnes, 1986), the use of videorecordings (Hunt *et al.*, 1984) and the introduction of patient guides. To our knowledge, none of these makes reference to this previously unreported complication.

We suggest that patients should be informed of this potential hazard. The use of catheters without funnelled ends is open to debate.

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Point of Technique

Alternative Techniques for Scrotal Reconstruction

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Two alternative techniques for reconstruction of the scrotum in total or near total skin loss following scrotal gangrene are described. The one-stage procedure employs bilateral bipedicle perineal flaps advanced medially to reconstruct the scrotum in patients without total loss of the perineal skin. The second technique is a three-staged procedure which uses superiorly based adductor skin flaps of the thigh. It is simple to plan and produces an excellent cosmetic result even in the presence of total scrotal skin loss.

Total scrotal skin loss in idiopathic gangrene of the scrotum is uncommon. However, when this occurs, "the testes bared to their tunica vaginalis hang suspended by their cords, shamefully exposed, though remarkably free of gangrene, inured and oblivious to their new surroundings and can be handled freely without causing the slightest discomfort" (Randall, 1920). Such was the appearance of the external genitalia of the 2 patients in this report. The provision of a cosmetically and functionally acceptable cuticular sac to house these exposed testes posed a reconstructive challenge.

Millard (1966), Robinson *et al.* (1946) and Hirshowitz *et al.* (1980) have described different methods of scrotal reconstruction in complete or near complete scrotal skin loss. This suggests that no single reconstructive procedure is satisfactory for all types and varying degrees of skin loss.

Case Reports

Case 1. An 81-year-old man with near complete loss of the scrotal skin and part of the penile skin was referred for skin cover after 3 months of conservative treatment for Fournier's gangrene. The exposed testes were hanging by their cords and the only scrotal skin left was a narrow irregular strip around the base of the scrotum.

Bilateral bipedicle perineal flaps were raised on either side of the external genitalia, advanced medially and sutured in the midline to cover the exposed testes. The lateral defects created by the medial advancement of the flaps and the penile skin loss were split skin grafted (Fig. 1). Despite initial post-operative sepsis, the procedure was a success as the testes were satisfactorily covered.

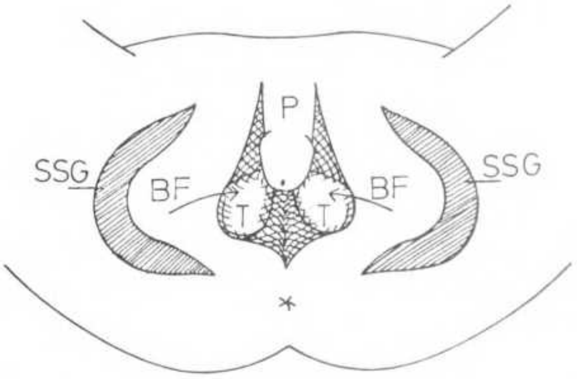

Fig. 1 Bipedicle perineal flaps raised on either side of the base of the exposed testes, advanced medially and sutured in the midline inferior to the hanging testes to form a new cutaneous sac. SSG = split skin graft. BF = bipedicle perineal flap. T = testis. P = penis.

Case 2. A healthy looking 27-year-old man with completely exposed testes and cords (Fig. 2) was referred for scrotal reconstruction. He had developed scrotal oedema followed by gangrene, the origin of which was undetermined. Eusol dressings were applied twice daily until clean granulation became evident and reconstruction of the scrotum was undertaken.

Under general anaesthesia, the patient was placed in the lithotomy position. Superiorly based cutaneous flaps over the adductor surfaces of both thighs were marked out (Fig. 3) and raised with lengths twice as long as the breadths. These were transposed, one posteriorly and the other anteriorly over the exposed testes and sutured together to form a skin sac enveloping the testes. To

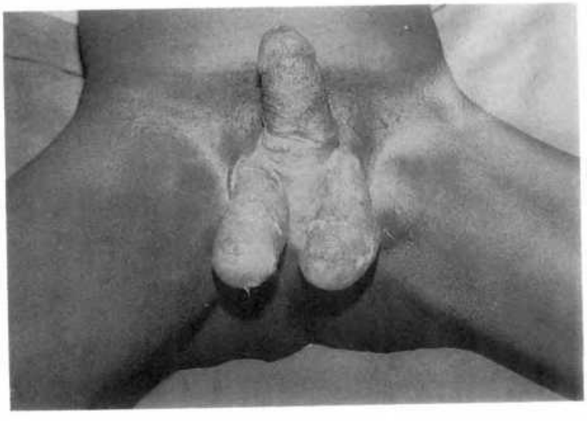

Fig. 2 Total scrotal skin loss in scrotal gangrene exposing both testes.

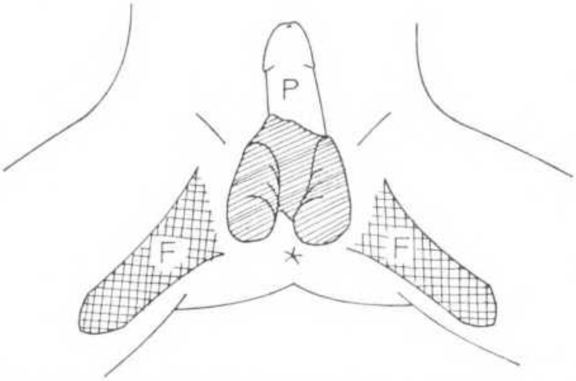

Fig. 3 Superiorly based cutaneous flaps over the adductor surfaces of both thighs used for reconstructing the scrotum. F = flap. P = penis.

encourage the flaps to overlap more effectively, the patient was returned to the usual supine position with slight abduction of the thighs.

Most of the defects created by raising the thigh flaps were sutured directly after undermining the wound edges. The proximal portions of the defects which could not be closed directly were split skin grafted. The pedicles were divided 3 weeks later and inset after a further week. The cosmetic appearance of the new scrotum (Fig. 4) was satisfactory. The patient has returned to his job as a taxi driver, has a normal sexual life and claims that his virility is unimpaired.

Comment

Patients with limited skin loss in Fournier's gangrene usually do well on conservative management alone, involving regular wet dressings. However, total or near total scrotal skin loss calls for a definitive reconstructive procedure. Altchek and Hoffman (1979) advised split skin grafting for denuded testes alone and burial of the testes in subcutaneous medial thigh pockets when the cords were also denuded. This approach recognises the technical difficulty in skin grafting the cords. In the absence of the dartos and the testes hanging separately, split skin grafts, apart from being less acceptable cosmetically, leave the patient aware of the lack of protection and therefore increased vulnerability.

Burying the testes permanently in medial thigh pockets makes the male external genitalia look incomplete and this may be an inhibiting factor in subsequent sexual relationships. This reaction may be stronger in the average African than in his Caucasian counterpart. Gonzalez-Ulloa (1963) and Tiwari *et al.* (1980) recognised this psychological instability in patients whose testes are buried in medial thigh pockets, where they may be exposed to higher temperatures because of proximity to thigh muscles.

Although Gonzalez-Ulloa (1963) used bipedicled perineal flaps, he buried the testes in medial thigh pockets in a preliminary operation. In addition, his perineal flaps used "M"-shaped incisions and no skin grafts were used to cover the defects created in raising these flaps. The bilateral bipedicle perineal flaps used to reconstruct the scrotum in the older of our 2 patients had the shape of "C" and mirror image of "C", thus forming a bracket. There was no need to bury the testes in thigh pockets and split skin grafts were used to cover the defects created by advancing the flaps medially. The reconstruction therefore had the advantage of being a one-stage procedure. Although the new scrotum looked tight initially, it stretched over the subsequent months and allowed the testes to hang loosely in the perineum.

Robinson *et al.* (1946), Millard (1966) and McDougal (1983) described scrotal reconstruction using medial thigh flaps preceded by implantation of the testes into medial thigh pockets. This

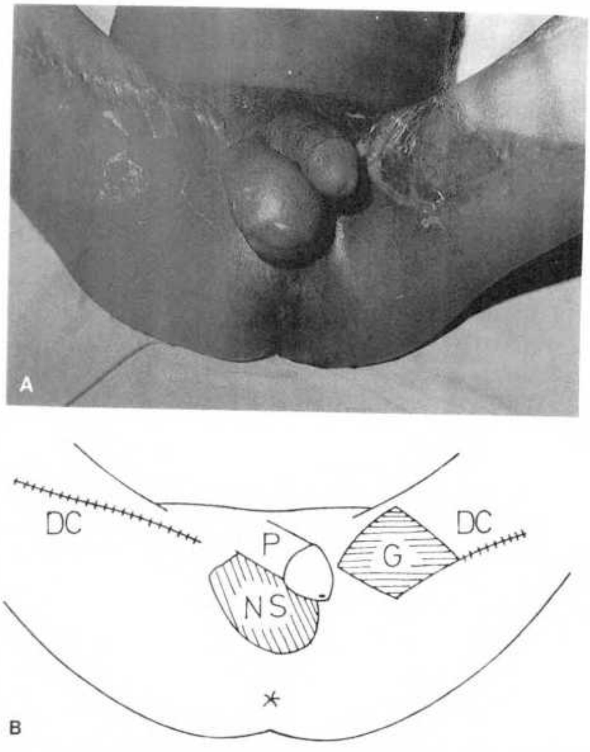

Fig. 4 (A) Reconstructed scrotum from thigh adductor skin flaps in same patient as in Figure 2. (B) Diagram of Fig. 4A illustrating suture lines of direct closure of the flaps' donor area. DC = direct closure. G = graft. NS = new scrotum. P = penis.

technique assumes poor vascularity of the flaps. The method of Millard (1966), which is a modification of the method of Robinson *et al.* (1946), emphasises that the flap needs at least one delay. Having embedded the testes, he gives the flaps the shape of ping-pong bats and when too tight to suture in the mid-line, are skin grafted posteriorly. However, the work of Har-Shai *et al.* (1984) demonstrated the presence of large and small nutrient arteries in the supermedial thigh flaps which include the superficial branch of the deep external pudendal artery and the musculocutaneous perforators of the medial circumflex femoral artery. The superiorly based adductor skin flaps of the thigh as described herein must have a similar arterial supply, since its proximal skin is the same skin as that used in the supermedial thigh flaps of Hirshowitz *et al.* (1980) and studied by Har-Shai *et al.* (1984). The procedure, though three-staged, is simple and produces a more normal appearance of the scrotum. The flaps are raised with only little subcutaneous tissues ensuring lower temperatures in the new scrotum. This is an advantage over the gracilis myocutaneous flaps employed by Westfall *et al.* (1981).

Douglas (1951) and Tiwari *et al.* (1980) used medial thigh flaps but these were based posteromedially. The flaps were therefore small, producing a rather diminutive scrotum without any suspension effect. However, it had the advantage of being a one-stage procedure. Based as they were, the flaps failed to use the good arterial supply to the adjacent skin to the scrotum, hence their smallness.

Earlier techniques of scrotal reconstruction have assumed that medial thigh flaps have poor vascularity. This has led to the use of tedious techniques of scrotal reconstruction with unsatisfactory cosmetic and psychological results. Har-Shai *et al.* (1984) showed that the supermedial thigh flap has a rich arterial supply. Adductor skin flaps of the thigh based superiorly have the same pedicle as the supermedial thigh flaps and so provide a larger area of skin for a cosmetically and functionally acceptable reconstructed scrotum.

Acknowledgement

I am grateful to Miss Wendy Aitken for typing the manuscript.

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Notices

British Association of Urological Surgeons

President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Annual Meeting: Scarborough. 10–13 July 1990

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

Second European Symposium on Stone Disease

Basel, Switzerland. 22–24 March 1990

Further information from: Mrs W. Heinzelmann, Urologische Klinik, Departement Chirurgie der Universität Basel, Spitalstrasse 21, CH-4031 Basel, Switzerland.

European Society of Paediatric Urology

Founded in June 1989, this Society aims to promote paediatric urology by means of clinical co-operation between paediatric urology departments (exchanges, prospective/randomised studies, data banks), research programmes, annual meetings (see Diary page), creation of an autonomous educational training programme and grants for training.

The President is Professor R. Scholtmeijer (Rotterdam), General Secretary Dr P. Mouriquand (Lyon), Treasurer Dr J. de Vries (Nijmegen), and the two Members of the Board are Dr R. Nijman (Rotterdam) and Mr P. Duffy (London).

For further information please contact Dr P. Mouriquand, "Le Dizenier", 11 impasse Mouillard, 69009 Lyon, France.

Bard Award

This award, made possible by the generosity of C. R. Bard International Limited, was given for the first time at the Annual Meeting in Bristol in 1979. The award will consist of the sum of £1500 and the Bard Silver Medal. The award will be given for the best essay submitted specifically for consideration for the award by members of the Association (non-members must be sponsored by a Full Member).

Essays should be based on original work on any topic connected with urological surgery, either clinical or experimental. The essay should include a review of the literature and the clinical implications of the work performed. A panel of three adjudicators will be nominated at the February meeting of Council each year. Submissions for the award should be made in triplicate by 1 March to the Honorary Secretary. The winning essay will be read during the Annual Meeting and should not exceed 20 minutes' duration.

Dantec Urology Prize

An annual prize is awarded by Dantec for the best scientific paper contributing towards the understanding of the function of the urinary tract, which has been accepted by a medical journal for publication in the United Kingdom. Special consideration will be given to papers relevant to clinical human urology. The prize will be known as The Dantec Award for Contribution to the Understanding of Urinary Tract Function. The prize will consist of a £400.00 travel voucher together with a token presentation gift. The prize will be presented at the BAUS Annual Meeting.

The competition is open only to graduates of British or Irish universities resident in the British Isles. Papers which have been published from 1 January to 31 December of the year preceding the award will be considered. Three members of BAUS Council will be nominated at the February meeting of Council to act as adjudicators. All entries, which must include a reprint of the paper in question, must be submitted by 1 April in the year of entry to the Honorary Secretary of the British Association of Urological Surgeons. The winner of the prize will be announced at the Annual Meeting, when the official presentation will be made.

Simpla Research Prize

The Simpla Research Prize was inaugurated in 1988 and consists of an annual prize of £1000.00 to support a clinical research project. Applicants should submit an abstract of not more than 500 words detailing the way in which, if successful, they would use the prize. These submissions should be made to the Honorary Secretary by 1 April. Entries will be judged by three members of Council nominated at the February meeting and the winner will be announced at the Annual General Meeting.

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Diary

1990

January 27– February 3	1990 Winter Urologic Forum Meeting. Steamboat Springs, Colorado, USA. Contract Linda Mace, Staff Assistant, Box 3707, Duke Medical Center, Durham, NC 27710, USA.
March 15–16	**Course in Urological Computing. Walton Conference Centre, Southern General Hospital, Glasgow. The second day of the course will be combined with the Fourth Annual Meeting of the Urological Computing Society. Contact Mr E. S. Glen, Urology Department, Southern General Hospital, Govan Road, Glasgow G51 4TF. Tel. 041 445 2466. Fax 041 445 3670.**
March 16	Early Prostatic Cancer—Which Treatment? Newport, Gwent. Contact Mr W. B. Peeling, Department of Urology, St Woolos Hospital, Newport, Gwent NP9 4SZ.
March 19	**BAUS One Day Symposium on Endoscopes, Video Equipment, Teaching Aids and Accessories. Whittington Hospital, London. Contact BAUS Office, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.**
March 21–23	International Conference on Early Prostatic Cancer. Stockholm, Sweden. Contact the WHO Collaboration Centre for Urological Tumours, Radiumhemmet, Karolinska Hospital, S-104 01 Stockholm, Sweden.
March 22–23	Journées Urologiques de l'Hôpital Necker, Paris, France. The topics will be Renal Artery Surgery and Pathology of the Testis and Spermatic Cord in Childhood. Contact Madame M. C. Brandt, Secrétariat du Professeur Cukier, Clinique Urologique, Hôpital Necker, 149 rue de Sèvres, 75743 Paris, France.
March 28–30	**Association of Surgeons of Great Britain and Ireland. Annual Meeting. Cardiff. Closing dates for abstracts 7th October 1989. Contact Ms Caroline Ross at the Royal College of Surgeons, Lincolns Inn Fields, London WC1. Tel: 01 405 3474**
April 22–26	18th Biennial Congress of the Urological Association of South Africa. Durban, South Africa. Contact Uro 1990, P.O. Box 17008, Durban 4013, South Africa.
April 27–28	Interactive Obstructive Uropathy. Manchester. Contact Mrs G. Trimble, Department of Urology, Withington Hospital, West Didsbury, Manchester M20 8LR
May 5–6	Athenian Days of Urology 1990. Athens, Greece. Contact Professor C. Dimopoulos, Department of Urology, Laiko Hospital, 115 27 Athens, Greece.
May 13–17	**Annual Meeting of the American Urological Association, New Orleans. Contact The Secretary, AUA, 1120 N Charles Street, Baltimore, Maryland 21201, USA.**
May 27–June 3	Urological Society of Australasia. 43rd Annual Scientific Meeting Darwin–Kakadu. Contact ASM Secretariat, Urological Society of Australasia, 145 MacQuarie St, Sydney 2000, Australia. Tel: 27 4461
June 9–10	Société Belge d'Urologie: 55th Congress. Brussels, Belgium. The topic will be "Medical Films on Urology". Contact Dr F. F. Wart, C.H.U-I.M.C.A.G., Division of Urology, Boulevard Zoe Drion 1, B-6000 Charleroi, Belgium.
June 12	First Annual Meeting of the European Society of Paediatric Urology. Amsterdam, The Netherlands. The topic will be Posterior Urethral Valves. Contact Dr P. Mouriquand, "Le Dizenier", 11 impasse Mouillard, 69009 Lyon, France.

June 13–16	Ninth Congress of the European Association of Urology. Amsterdam. Contact QLT Convention Services, Keizersgracht 792, 1017 AC Amsterdam, The Netherlands. Tel: 010 31 20261372
June 24–28	Canadian Urological Association Meeting, Vancouver, British Columbia, Canada. (To be held jointly with members of BAUS). Contact Dr J. P. Collins, Ottawa Civic Hospital, 1053 Carling Avenue, Ottawa, Ontario K1Y 4E9, Canada.
July 10–13	BAUS Annual Meeting, Spa Conference Centre, Scarborough. Contact Secretariat, Royal College of Surgeons, Lincolns Inn Fields, London WC1. Tel: 01 405 1390
September 9–11	Biannual Conference of International Society for Dynamics of the Upper Urinary Tract. Stockholm, Sweden. Contact Anne-Charlotte Kinn, Department of Urology, St Görans Sjukhus, 112 81 Stockholm, Sweden.

Courses which are recommended for Senior Registrar Education are marked with (SR).

All 'BAUS–associated' meetings/courses are printed in bold.

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REVIEW

Fertility after Torsion of the Spermatic Cord

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Spermatogenesis Following Torsion

One might expect normal testicular function after timely release of an acute torsion of the spermatic cord. For endocrine function this probably is the case, at least in so far as the sex hormone levels in the blood are concerned. But for exocrine function, i.e., spermatogenesis, not only is the affected testis frequently impaired but there also appears to be an abnormality of the opposite gland, as revealed by post-operative semen analysis. If it is assumed that one healthy testis is enough to maintain normal fertility, as is probably the case in man and certainly in the rat (Mauss and Hackstedt, 1972), the contralateral testis must therefore be either primarily defective or secondarily damaged during or after the episode of torsion.

Testicular exocrine function after torsion was first examined by Krarup in 1978. Semen samples were analysed from 19 patients between 3 months and 13 years after operation for unilateral torsion, and only 1 sample was found to be within normal limits. Although sperm concentrations varied greatly ($0.9-131 \times 10^6$/ml), 36% of patients had counts of less than 20×10^6/ml, *i.e.* levels consistent with subfertility. The sperm concentration was lowest among those patients who had undergone orchiectomy, and even those with a high sperm concentration had many dead or abnormal forms.

Since this initial study, several other groups (including ourselves) have confirmed abnormal sperm production in patients up to 12 years after the original episode of torsion (Bartsch *et al.*, 1980; Dondero *et al.*, 1980; Mastrogiacomo *et al.*, 1982; Thomas *et al.*, 1984a; Fraser *et al.*, 1985; Puri *et al.*, 1985; Awojobi and Nkposong, 1986; Anderson and Williamson, 1986). Semen analysis in a total of 240 patients has shown that 37% have an abnormally low sperm concentration (<20 million/ml), 56% have too few motile sperm (<40%) and 53% have too many abnormally shaped spermatozoa (>50%). Bartsch *et al.* (1980) noted that among patients whose duration of torsion exceeded 24 h, those who came to orchiectomy had higher sperm counts than those who had undergone detorsion and bilateral orchiopexy. Our initial finding that the total motile sperm count in patients with previous torsion bore a close correlation to the duration of previous torsion (Thomas *et al.*, 1984a) was not confirmed by subsequent work in our own laboratory or elsewhere (Fraser *et al.*, 1985; Anderson and Williamson, 1986).

The frequency of torsion of the spermatic cord suggests that it could be an important cause of male infertility. It is the second most common surgical emergency in young men in Britain, affecting 1 in every 158 by the age of 25 years (Anderson and Williamson, 1988). Only prompt diagnosis and operation can save the affected testis from rapid infarction or slow ischaemic atrophy. Perhaps of greater concern, however, is the effect of torsion on contralateral testicular function. A clear understanding of the reason for this impaired spermatogenesis is crucial for proper management of this common condition. The question has been examined in both experimental animals and man.

Experimental Studies

Effect on the opposite testis

It is debatable whether experimental torsion of the spermatic cord will damage the germinal epithelium of the opposite testis. Our preliminary study, using the Johnsen scoring system to assess spermatogenesis, did suggest contralateral damage after unilateral torsion in rats, but sample sizes were small and differences slight (Thomas *et al.*, 1984b). A similar study suggested that the impaired spermatogenesis and decreased size of seminiferous tubules were

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reversible with time (York and Drago, 1985). Although minor histological changes can be seen in the opposite testes of rats and rabbits after 1 to 4 weeks (Harrison *et al.*, 1981; Wallace *et al.*, 1982; Nagler and de Vere White, 1982; Cerasaro *et al.*, 1984; Sade *et al.*, 1988), it is difficult to separate the specific effects of torsion from the non-specific inflammatory changes that follow operative trauma to the scrotum. A sensitive assessment of damage after unilateral torsion in the rat was provided by flow cytometric examination of DNA histograms from single cell suspensions of the contralateral testis. The presence of abnormal histograms in up to 80% of animals is difficult to interpret, however, since the rats were examined only 2 weeks after the episode of torsion. The additional finding of impaired fertility over the ensuing 6 months is perhaps of greater significance (Nagler *et al.*, 1984). A more thorough histological examination included 10 different measurements of damage, but only revealed significant differences in the "disarray of germ cell layers" (a difficult change to quantify) and Leydig cell proliferation when compared with sham operated animals (Cosentino *et al.*, 1985).

All of these reports have identified contralateral damage to the germinal epithelium following unilateral torsion, but discrepancies in the results weaken the overall conclusion. Thus some have shown that the contralateral testicular damage may be ameliorated or prevented by orchiectomy (Nagler and de Vere White, 1982; Cosentino *et al.*, 1985; York and Drago, 1985), but others disagree (Wallace *et al.*, 1982). Changes were seen in the opposite testis in prepubertal animals in one report (Cosentino *et al.*, 1985) but not in another (Nagler *et al.*, 1984; Henderson *et al.*, 1985). Unfortunately, testicular ischaemia and actual torsion have been used interchangeably by some workers (Harrison *et al.*, 1981; Nagler *et al.*, 1984), while others have found contralateral effects after testicular torsion but not after ischaemia caused by simple ligation of the testicular artery (Cerasaro *et al.*, 1984).

The negative data are arguably more clear-cut. Several workers, using similar experimental models, have failed to demonstrate either structural or functional damage to the opposite testis after unilateral torsion. Thus no tubular damage was encountered in the contralateral testis of Chinese hamsters 1 week, 1 month or 6 months after unilateral spermatic cord torsion, and active spermatogenesis was observed at 6 months (Henderson *et al.*, 1985). A large study in rats showed no alterations in the histological appearances of the opposite testis, no reduction in sperm concentration or motility and no compromise in animal fertility after unilateral torsion (Saltzman *et al.*, 1984). Similarly, normal testicular structure and function was demonstrated in the immune-sensitive Lewis rat by means of histology and epididymal sperm concentrations and motility at 30 and 60 days (Turner, 1987). Although Janetschek *et al.* (1988) reported a 50% decrease in sperm output 8 weeks after unilateral torsion in the rat, quantitative morphological assessment of the unaffected testis employing stereological techniques showed nothing other than an increase in Leydig cells. Lastly, there was no abnormality in the opposite testis on gross or histological examination 1 to 6 months after torsion in another study and no reduction in vas deferens sperm counts (Ryan *et al.*, 1988). Furthermore, rats with absent sperm production from the ipsilateral (*i.e.* twisted) testes were all fertile, testifying to the competence of contralateral spermatogenesis.

In summary, no clear consensus emerges from animal studies concerning the response of the "normal" contralateral testis to unilateral torsion of the spermatic cord. Although several workers have been unable to demonstrate any loss of structure or function, there are too many data supporting such an effect to be ignored. It is therefore necessary to consider possible causative mechanisms.

Sympathetic orchiopathia

If the phenomenon of damage to the opposite testis is controversial, possible immunological mediation of the injury is just as contentious. It has long been known that injection of homologous or autologous testicular antigens can lead to production of specific anti-testis antibodies; affected animals develop autoimmune orchitis culminating in germinal cell destruction and azoospermia (Freund *et al.*, 1953). Under these circumstances γ-globulin has been shown to penetrate the blood-testis barrier and enter the seminiferous tubules (Johnson, 1970), suggesting that the damage to the testis is immunologically mediated. Evidence for an immunologically mediated "sympathetic orchiopathia" following unilateral testicular ischaemia was first provided by Harrison *et al.* (1981). They identified increased cytotoxic antisperm antibody in rat serum plus antibody deposition in the contralateral testis (on indirect immunofluorescence). The significance of these results is uncertain, since normal rat serum is cytotoxic to sperm and the rat testis has a degree of natural fluorescence. Anti-sperm antibodies can be found in rat serum following true testicular torsion, using an indirect immunofluorescence technique (Merimsky *et al.*, 1984). Our preliminary study also found spermagglutinating antibodies in rats with detorsion or delayed orchiectomy after torsion but not in those that had undergone immediate orchiectomy after a similar period of torsion. The implication here is that over a period of time the dying testis will autoimmunise the rat. Following examination of the sera from rats with an immunoblotting technique against spermatozoal membrane proteins, Ryan and Fitzpatrick (1986) demonstrated a rising antibody titre 1 week after acute torsion. However, these antibody levels had markedly decreased within 1 month and disappeared by 6 months. In a further study, direct immunofluorescent histochemistry revealed no evidence of tissue fixation of these circulating spermatozoal autoantibodies in the contralateral testis at 1 month (Ryan *et al.*, 1988).

Once again there is a great deal of evidence to the contrary. Immunological mediation of damage to the opposite testis after unilateral torsion could not be confirmed in 2 studies; one used an immunoperoxidase method to detect immunoglobulin deposition in rat testis (Wallace *et al.*, 1982); the other used an enzyme-linked immunosorbent technique to detect anti-sperm antibodies in rabbit serum (Cerasaro *et al.*, 1984). Direct immunofluorescence staining of the contralateral testis after torsion was similarly negative (Saltzman *et al.*, 1984; Henderson *et al.*, 1985). It therefore seems that any antigenic stimulation of the immune system from the twisted testis is only transient in nature. It may be that animal models are an inappropriate way in which to examine the human problem. In laboratory animals the testis is normal and probably not prone to spontaneous torsion. In man, either or both testes may be abnormal in some way from the outset. Nevertheless, the relative paucity of experimental changes in the opposite gland does not suggest a true sympathetic orchiopathia.

Clinical Studies

Reasons for post-torsion subfertility

Since at least half of the patients with previous torsion of the spermatic cord are subsequently found to have poor sperm counts, torsion appears to be a bilateral disease. The manner in which the opposite testis is involved is of fundamental importance from the therapeutic point of view. The standard surgical teaching to preserve the testis if there is a reasonable chance of viability might well be inappropriate if the injured organ were to cause antibodies that damaged the opposite side. A number of possible explanations can be advanced to explain the bilateral testicular exocrine failure that follows unilateral torsion.

1. The prophylactic manoeuvre of exploring and fixing the opposite testis at the time of operative correction of torsion could theoretically be injurious. Against this hypothesis, Krarup (1978) found abnormal semen analysis alike in patients with or without contralateral orchiopexy at variable intervals after the acute episode. Animal studies have also shown that contralateral orchiopexy alone does not impair spermatogenesis (Nagler and de Vere White, 1982).
2. A testis that has undergone torsion might damage its "normal" fellow by producing some toxic substance. Since there is some experimental evidence in favour of anti-spermatozoal humoral immunity, a similar process might occur in man. The testis is an immunologically privileged site: its germinal epithelium is normally protected from the immune system by the blood-testis barrier, but this barrier might be destroyed by an ischaemic injury. Antigenic material from the necrotic testis would then escape into the blood, stimulating the production of auto-antibodies capable of attacking the unaffected testis and causing a sympathetic orchiopathia (Wallace *et al.*, 1982).

Evidence for sympathetic orchiopathia in man is even more fragmentary and unsatisfactory than it is in experimental animals. There is one case report of a man with a low sperm count and cytotoxic anti-sperm antibodies in the serum 9 months after "silent" testicular torsion; removal of the atrophic testis resulted in disappearance of the antibodies and return of the sperm count to normal (Laurenti *et al.*, 1978). Circulating anti-sperm antibodies were previously demonstrated in up to 20% of patients at variable periods after testicular torsion (Dondero *et al.*, 1980; Mastrogiacomo *et al.*, 1982; Zanchetta *et al.*, 1984), but recent studies have not confirmed this finding. Although 36 of 47 patients studied 2 to 10 years after torsion had abnormalities of exocrine or endocrine gonadal function, none showed evidence of testicular autoimmunisation using standard assays of sperm agglutination or immobilisation in serum or seminal plasma (Fraser *et al.*, 1985). Another 11 patients followed for 3 to 6 months after operative relief of acute torsion showed not even the transient development of sperm antibodies, and such antibodies could not be detected in the serum of men in whom a twisted testis had been left *in situ* (Puri *et al.*, 1985). Our own results confirm these negative reports, with anti-sperm antibodies being found in the serum of only 9% of patients in a prospective study of 32 patients up to 6 months after acute testicular torsion (Anderson and Williamson, 1986). It therefore seems most unlikely that autoimmunisation and sympathetic orchiopathia can account for the impaired spermatogenesis that follows unilateral torsion of the cord.

3. Perhaps the impaired spermatogenesis observed after torsion originates before the acute event. Both testes might be progressively damaged by recurrent episodes of transient ischaemia as the "bell-clapper" twists and untwists. The high investment of the tunica vaginalis that predisposes to torsion is generally symmetrical, and at least one-third of patients with torsion complain of previous attacks of pain and swelling usually on the same side (Anderson and Williamson, 1988). It seems a little unlikely that asymptomatic twisting of the spermatic cord could cause such severe functional damage in man. Moreover, the results of our own prospective study suggest that this is not the only factor responsible for post-torsion oligozoospermia. Among 32 patients with acute torsion, 12 admitted to previous episodes of scrotal pain; 7 of these had normal contralateral testicular biopsies taken at the time of operation for acute torsion and normal sperm counts 3 to 6 months later (Anderson, 1987).
4. There might be a bilateral congenital defect in spermatogenesis associated with the bilateral "bell-clapper" anomaly of the tunica vaginalis, and this is only brought to light by the episode of torsion. In one study, tissue damage was described in contralateral testicular biopsies obtained from 7 patients at the time of torsion (Horica *et al.*, 1982). In another, retrospective examination of biopsies taken from 38 patients at the time of operation for torsion showed abnormalities in 53% (Hadžiselimović *et al.*, 1986). In prepubertal boys the number of spermatogonia per seminiferous tubule was reduced, and following puberty there were fewer late spermatids in both the twisted and the non-twisted testis. Thus testes prone to torsion seem to have a subtle pre-existing abnormality of spermatogenesis. The situation is analogous to the bilateral impairment of sperm production that explains low sperm counts in unilateral cryptorchids (Woodhead *et al.*, 1973). Since cryptorchidism itself predisposes to torsion (Anderson and Williamson, 1988), congenital anomalies of the testis appear to be multiple.

The bilateral defect

Our own prospective study of 32 patients with acute testicular torsion was designed to test the hypothesis that impaired spermatogenesis might accompany the abnormal development of the processus vaginalis in testes prone to torsion (Anderson and Williamson, 1986). Contralateral testicular biopsy at the time of torsion showed evidence of partial maturation arrest of spermatogenesis in 57%; arrest occurred mainly at the late spermatid stage of development. In those testes with this abnormality, the seminiferous tubules were smaller in diameter, the Johnsen score was reduced and there were fewer late spermatids per seminiferous tubule; 46% of these patients had an abnormally low sperm concentration following torsion and the degree of oligozoospermia correlated closely with both the Johnsen score and the number of late spermatids per seminiferous tubule. All of those patients with normal testicular histology had sperm concentrations within the normal range, while no correlation was observed between the duration of torsion and the subsequent sperm count; 40% of patients with oligozoospermia also had a raised serum FSH level. Since FSH increases *pari passu* with destruction of the germinal epithelium, this finding lends further support to the concept of defective spermatogenesis in abnormally mobile testes.

Implications for Surgical Practice

These results clearly diminish the relevance of autoimmunisation in the development of post-torsional oligozoospermia in man; the largely negative auto-antibody data are consistent with this view. The poor sperm counts seen after unilateral torsion owe more to a pre-existing defect than to damage induced in the opposite testis as a consequence of unilateral torsion. Congenital dysplasia of the germinal epithelium seems the most plausible explanation, though we cannot discount the possibility of cumulative damage from recurrent minor episodes of twisting. Although we can find no clear data on the subject, personal experience of patients with only one functioning testis who request vasectomy suggests that there is ordinarily a considerable functional reserve. However, such reserve may well be absent in "bell-clapper" testes, so that further ischaemic injury would precipitate subfertility. We therefore recommend preservation of all testes with a reasonable chance of viability, particularly as we have failed to demonstrate antibody production thereafter. However, if the testis is irretrievably damaged—and this is likely after 12 h of unrelieved torsion—its retention carries an appreciable risk of sloughing and delayed wound healing (Anderson and Williamson, 1988).

The prognosis for patients who are oligozoospermic following torsion is difficult to assess. Most workers have used a figure of 20×10^6/ml as the lower limit to distinguish normal from abnormal sperm concentrations, but this level may need to be revised in the light of more recent studies. Semen analysis from fertile men before vasectomy indicates that a figure of 10×10^6/ml may be more relevant (Smith and Steinberger, 1977). Although half of the patients in our prospective study were oligozoospermic by conventional criteria following torsion, only 16% had sperm counts lower than 10×10^6/ml (Anderson and Williamson, 1986).

A greater cause for concern is provided by recent reports of carcinoma *in situ* in testes from infertile men (Hargreave, 1986). Infertile men at risk of carcinoma *in situ* typically have a low sperm concentration (less than 20×10^6/ml) and reduced testis volume. They may also have a history of testicular pain associated with first decrease and then increase in testicular size. To date there has been no report of carcinoma *in situ* in testicular biopsies taken at the time of contralateral orchiopexy, although there is at least a 3-fold increase in the risk of testicular cancer in association with torsion of the testis (Chilvers *et al.*, 1987).

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Epidemiological Study of Urinary Tract Stones in a Northern Italian City

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Summary—An epidemiological study of stone disease in a Northern Italian city was carried out by means of a postal questionnaire mailed to 6000 individuals (2.5% of the entire population).

It was found that the incidence of stone disease was comparable to that of industrialised Western Europe. There was a relationship between stone disease and gout and stone disease and a positive family history. The frequency of uric acid stones was high (26.5%). Stone-formers showed no alimentary differences from non-stone formers apart from the use of spices and herbs.

Stone-formers used less water from public aqueducts and more uncarbonated mineral water, but only 19% of these drank at least 2 litres a day.

There is considerable variation in the incidence of urinary tract stones and their chemical composition in populations from different points of the socio-economic scale (Peacock and Robertson, 1980; Asper, 1984). Significant differences also exist between the incidence and the number of admissions to hospital for this condition within the same area where socio-economic standards are high (Johnson *et al.*, 1979; Juuti and Heinonen, 1979; Bengtsson *et al.*, 1980; Robertson and Peacock, 1981; Tschöpe *et al.*, 1981; Hiatt *et al.*, 1982; Vahlensieck *et al.*, 1982; Ljunghall, 1987).

Epidemiological studies have been carried out (Pavone-Macaluso and Miano, 1979; Marangella *et al.*, 1982) which show vast differences in the frequency and chemical composition of renal stones between North and South Italy. We are unaware of any Italian studies that have evaluated, in a population of stone formers, the adherence to dietary measures such as a reduction in calories and animal proteins and an increase in water intake.

The aim of this study was to determine the incidence of urinary tract stones in an industrial Northern Italian city, with a social scale comparable to that of most Western European cities.

We also analysed the compliance of a population affected by renal stones to generally recommended dietary preventive measures and sought to establish a correlation between renal stones, social and hereditary factors and other diseases.

Methods

Selection of sample group

From the anagraphic register of the population of Parma (n = 238,007) a random sample of 6000 was chosen (2.5% of the population). The software package SAS (SAS User's Guide: Basics, Cary, USA) was used to generate 6000 random numbers between 1 and 238,007. Each of these random numbers was paired in progression with the register numbers of the population. The routine used has the mathematical expression (Lewis *et al.*, 1969; Kennedy and Gentle, 1980).

$$u_{(n+1)} = K\,u_n \pmod{2^{31}}$$

where:

$u_{(n+1)}$ = random number (n + 1)th
u_n = random number (n)th
K = constant multiplier chosen so as to obtain a long sequence of random numbers without repetition (in our case K = 16807).

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The population and the sample were distributed normally with respect to age (Kolomogorov's D test, $P<0.01$) and the average ages were not significantly different (41.6±22.2 against 41.4±22.2 years; T-test group=0.916, *P* NS).

A 30-question questionnaire was mailed to these 6000 individuals. The first 17 questions were general and concerned personal data (age, sex, weight, civil status, profession, sporting activities), dietary habits (quality and quantity of liquids and foods) and diseases (renal colic and calculi, hypertension, gout, diabetes, biliary colic, arthritis, arthrosis, ulcer and hepatic, cardiac or respiratory disease).

The next 13 questions were directed specifically to those who suffered from colic or urinary tract calculi and concerned the recurrence of colic and calculi, composition of the stones, diagnostic tests, surgical procedures and preventive measures. Before the final draft, a proof of the questionnaire was completed by a preliminary sample of the population from different cultural levels. The existence of the study was publicised by local radio and television stations and the local press.

Analysis of group answers

The total number of questionnaires returned was 2460 (41%), of which 11 were discarded because they were badly completed; 45 were returned incomplete and 2404 were completed (1% of the entire population).

The 2404 valid answers were normally distributed with respect to age (Kolomogorov's D test, $P<0.01$), although the average age was different from that of the general population (F=6.11, $P<0.05$). On excluding individuals over 80 years of age (almost 3% of the population and 2% of the answers), the differences in average age and behaviour disappeared, indicating that fewer elderly people responded to the questionnaire.

A comparison between population gender and replies showed no significant differences (chi-square test=0.80, *P* NS). Since the number of questionnaires returned was 41%, and using the same procedure for the sample, 500 people who owned telephones were extracted from the anagraphic register. For children the telephone numbers were obtained by using the family address. It was possible to interview 480 people and ascertain if they had ever had colic, either with or without the passage of calculi.

It is important to note that since the questionnaire was anonymous, it is possible that some individuals who had earlier answered by mail were also interviewed by telephone. This should be less than 1% and, in the worst hypothesis, 5 people could have been interviewed by both methods.

Assessment of data

The data were analysed with the software package SAS (Statistical Analysis System) running on an IBM 4381 hardware system. A comparison of the age distribution in the population was carried out using the F test (analysis of variance). A comparison between parametric factors was performed using the Student's *t* test groups and a comparison between non-parametric factors was carried out using the chi-square test. A *P* value <0.05 was considered significant.

Results

Analysis of the information received from the questionnaires involved the groups listed in Table 1. The results indicated that 10.3% of the population of Parma suffered from colic or calculi and that 6.1% had had at least 1 stone. This prevalence can be compared with that of other diseases (Fig. 1), demonstrating that kidney stones play an important role in population morbidity. The prevalence of renal colic and stone passage in the 480 persons interviewed by telephone was 10.7 and 5.5% respectively.

Analysis of the answers from people who had suffered colic or colic and stones (249) and those who had not (2155) revealed significant differences with regard to age (50±15 versus 40±20 years, $P<0.001$), body weight (70±14 versus 64±16 Kg, $P<0.001$) and sex distribution (60.6% male and 39.4% female versus 47.3% male and 52.7% female, $P<0.001$). These differences made it impossible to make any direct comparison between the 2 populations. In order to eliminate interference by age and sex, we randomly selected from the sample

Table 1 Groups Involved in the Study

1	Entire USL 4 population of Parma: 238,007
2	Questionnaires sent: 6000 (2.5% of population)
3	Questionnaires returned complete: 2404 (1% of population)
A	Subjects without renal colic or stones: 2155
B	Subjects with renal colic or stones: 249
C	Subjects with 1 or more stone episodes: 149
D	Subjects with renal colic but no stone episodes: 100
E	Patients claiming to have taken preventive measures: 139
F	Patients claiming to have taken no preventive measures: 86
	Control group B randomly selected from A: 804
	Control group C randomly selected from A: 863
	Control group E randomly selected from A: 896
	Subjects interviewed by telephone: 480

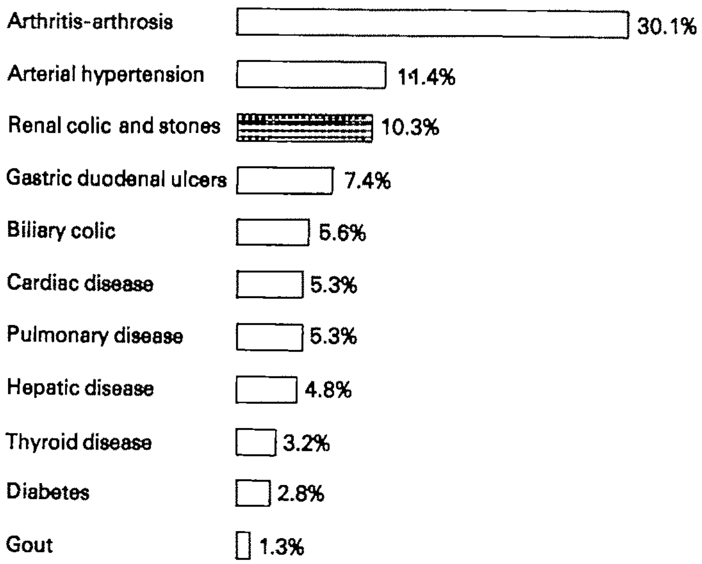

Fig. 1 Incidence of diseases in population of Parma.

without renal colic or calculi a sample normalised for age and sex with the group with colic or calculi; this control group was composed of 804 people. Table 2 summarises the differences between these groups. It can be seen that patients suffering from calculi or renal colic included a high percentage of married subjects; there was a high consumption of mineral water, a reduction in the use of herbs and spices and a high incidence of gout and family history of renal stones. Statistical comparison between populations which had passed stones (n = 149) and the control group (n = 863), also normalised for age and sex, confirmed these differences.

Of the 249 subjects with colic and calculi, 139 claimed to have taken preventive measures (diet and increased water intake). To verify which measures were really adopted, the responses from this group were compared with those from a control group (n = 896), normalised for sex and age. No significant differences emerged regarding dietary habits, but significant differences were found in the qualitative and quantitative consumption of water (Table 3).

The answers to the second part of the questionnaire (reserved for patients with urinary tract stones) showed that relapses were more frequent in patients who had taken no preventive measures (61%) than in those who had done so (52%), although the difference was not statistically significant ($P = 0.3$).

The following salient points also emerged. In general, relapses affected 54% of patients; 64% experienced their first episode of colic before the age of 40 years, with a peak at 30 years; 78% underwent urographic tests and 3.6% refused

Table 2 Summary of Differences between Groups

	Subjects with renal colic or calculi (n=249) (%)	*Control group (n=804) (%)*	*P*
Civil status			
Single	15	22	0.001
Married	81	69	
Widowed	4	9	
Water (quality)			
Mineral (carbonated)	38	40	0.004
Mineral (uncarbonated)	40	30	
Aqueduct	22	30	
Water (quantity)			
None	13	17	0.001
At least 1 litre	74	77	
At least 2 litres	13	6	
Consumption of herbs and spices			
Yes	0	2	0.05
No	100	98	
Presence of gout			
Yes	4.8	1.2	0.001
No	95.2	98.8	
Family history of kidney stones			
Yes	34	14	0.0001
No	66	86	

Table 3 Differences between Groups in Terms of Preventive Measures

	Subjects with renal colic or calculi taking preventive measures (n=139) (%)	*Control group (n=896) (%)*	*P*
Type of water consumed			
Mineral (carbonated)	33	40	0.001
Mineral (uncarbonated)	53	30	
Aqueduct	14	30	
Amount of water consumed daily			
None	11	17	0.001
At least 1 litre	70	77	
At least 2 litres	19	6	

through fear of the procedure; 11.5% underwent surgery for urinary tract calculi.

Figure 2 shows the distribution of patients with respect to stone composition as described in their answers. It should be noted that every patient who expelled renal stones and brought them to the laboratory received a chemical analysis report for reference. The proportion of patients who formed uric acid stones was very high (26.5%); considering the fact that 36.3% of those who replied said that they did not know the chemical composition of their stones, it is probable that some of them may also have had uric acid calculi.

Discussion

As in similar studies (Robertson *et al.*, 1984), the main problem with postal questionnaire surveys is that the patients will probably answer more readily than others. In the present study, however, statistical analysis demonstrated that the age and sex distribution between the responders and the general population was almost identical: this suggests that the sample replying was truly representative of the general population. Furthermore, only a slight bias in colic and stone prevalence was deduced from the answers of those interviewed by postal questionnaire and those by telephone.

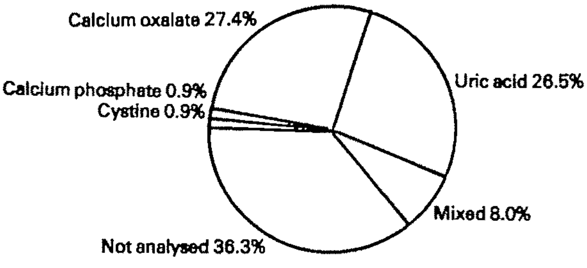

Fig. 2 Distribution of patients (Group C, Table 1) according to chemical composition of stones.

This study indicates that about 10% of the population of Parma may encounter an episode of renal colic, followed by expulsion of calculi in 60%. Among the diseases analysed, renal colic was the third most common, after arthritis/arthrosis and arterial hypertension. Parma has a prevalence rate of 5.3 to 6.1% for urinary tract calculi, which is slightly higher than that found in other Northern European cities with similar social and economic standards of living (Vahlensieck *et al.*, 1982; Robertson *et al.*, 1984).

In common with Vahlensieck *et al.* (1982), we found a low frequency of stones in patients under 15 years of age (2.7% of all cases) and in those aged over 70 (10%).

With regard to sex distribution, a slight male prevalence was apparent; the M/F ratio was 1.5, as is the case in Northern Europe. The percentage of patients with uric acid stones was particularly high (26.5%). This is not unusual for Italy (Pavone-Macaluso and Miano, 1979) and calls to mind epidemiological risk factors such as alcohol consumption and other dietetic habits peculiar to the region (Robertson *et al.*, 1979; Zechner *et al.*, 1982; Robertson, 1984). An analysis of calculi, family history and social factors revealed that a positive family history and the civil status "married" were associated with a particularly high incidence among the population with renal colic or calculi. On the other hand, no difference was observed regarding body weight, height, work or sporting activities.

In a survey of men in Leeds, Robertson *et al.* (1984) noted an association between calculi and other common diseases (biliary calculi, hypertension, backache, arthritis and gout). In Parma the only statistically significant association was between calculi and gout, although our study concerned both men and women. Our patients did not follow the usual dietary advice for renal stones, except for the avoidance of spices and herbs. In particular, there was no difference in the consumption of meat and other animal proteins between stone-formers and the rest of the population. This suggests that either patients were not made aware that animal protein is a risk factor for further relapses (Robertston *et al.*, 1979) or they failed to act on this advice. A different behaviour pattern was seen regarding water intake; the population with calculi used less water from public aqueducts and more uncarbonated mineral water. Only 19% of patients took adequate amounts of water, 2 litres/day being the minimum amount required for effective prevention. This suggests that most stone-formers interpreted prevention as the consumption of uncarbonated mineral water, but in quantities which were inadequate. This probably explains why the relapse rate was no different between subjects who took preventive measures and those who adopted measures such as increased water consumption.

It was concluded that in an industrialised city in Northern Italy with a high standard of living, the frequency of renal stones in the general population was high and slightly greater than that reported in similar studies involving other Northern European cities. The composition of the calculi was different, with uric acid stones more frequent than in Northern Europe. The study also revealed links between calculi, gout and familial incidence.

It was deduced that stone patients did not follow a different dietary style from the rest of the population except for a high consumption of uncarbonated mineral water, with 80% of those interviewed consuming insufficient quantities to prevent recurrence.

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Single Urine Sample Diagnosis. A New Concept in Stone Analysis

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Summary—A method of single urine sample crystal diagnosis after extracorporeal shockwave lithotripsy (ESWL) is described.

The collection of stone fragments large enough for diagnosis after piezoelectric ESWL may prove difficult owing to the size of the particles passed and the practical problems of patients filtering their own urine. Stone diagnosis is obtained from fragments in many laboratories using infra-red spectroscopy (IRS). We investigated an alternative technique, combining scanning electron microscopy (SEM) with X-ray energy dispersive spectroscopy (XES), for the analysis of urine samples after ESWL.

Patients and Methods

More than 25 ml of urine was collected from each lithotripsy patient investigated. The urine samples were centrifuged (2000 rev/min) and the supernatant fluid removed. Distilled water was used to wash the residue to cause lysis of red blood cells. The mixture was centrifuged (2000 rev/min) and a drop of deposit placed on a perspex slide. The slide was dried and carbon coated to remove any electronic charge prior to examination by SEM and XES (Khan and Hackett, 1987).

Results

After studying 30 urine samples using the combination of SEM and XES, it was apparent that crystals could be found consistently in urine taken from patients immediately after Wolf piezoelectric ESWL. Figures 1, 2, and 3 show the characteristic scanning electron microscopic appearances of brushite, calcium oxalate and calcium carbapatite with triple phosphate crystals respectively. Figures 4, 5, 6 and 7 show typical X-ray emission spectroscopy traces from brushite, calcium oxalate, calcium carbapatite and triple phosphate respectively. In 11 patients where fragments were available for conventional IRS, a direct comparison was possible between the results of IRS of fragments and the analysis of single urine samples after ESWL using the combination of SEM and XES. The results of this study are summarised in the Table.

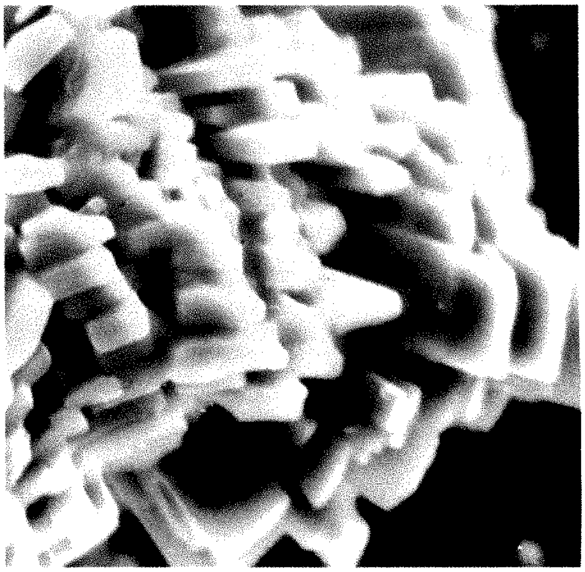

Fig. 1 Scanning electron microscope appearances of brushite (×660).

Based on a Poster Demonstration at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

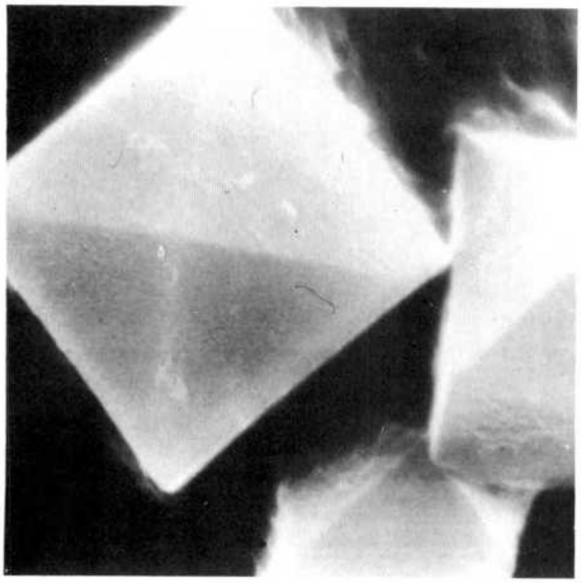

Fig. 2 Scanning electron microscope appearances of calcium oxalate (× 4000).

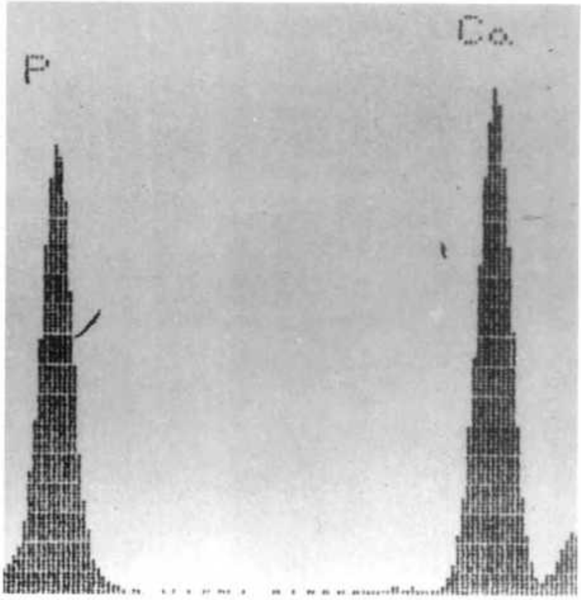

Fig. 4 X-ray emission spectroscopy traces from brushite.

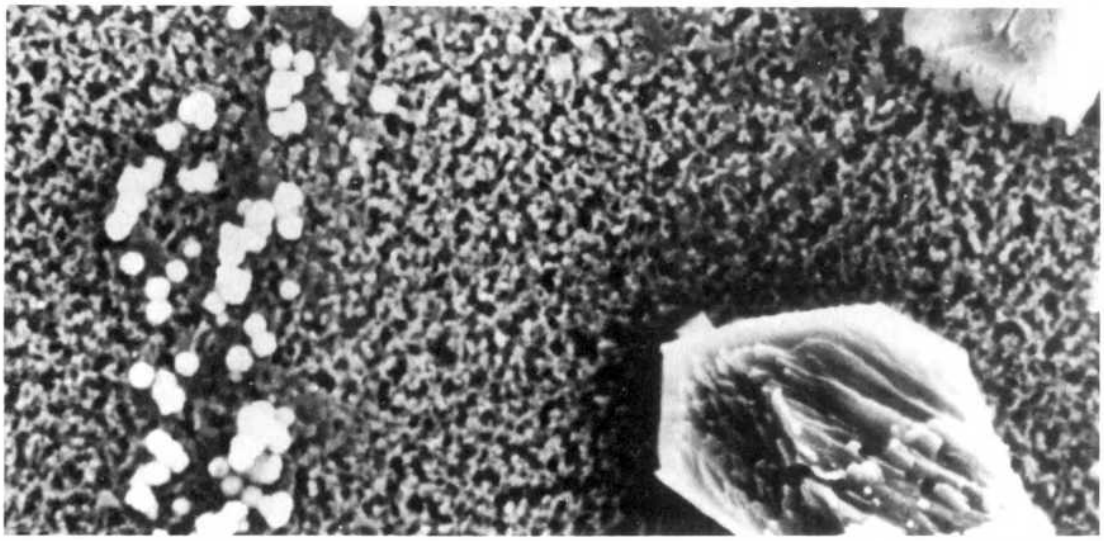

Fig. 3. Scanning electron microscope appearances of calcium carbapatite (left) and triple phosphate (right) (× 1500).

Discussion

SEM and XES have been described previously as techniques for identifying urinary crystals (Finlayson and Reid 1978; Hesse *et al.*, 1981; Thrall *et al.*, 1985; Khan *et al.*, 1986; Khan and Hackett, 1987). We believe that this is the first study comparing the combination of SEM and XES analysis of single urine samples after ESWL with IRS analysis of stone fragments. Diagnosis using IRS requires at least 1.5 mg of stone fragments. Patients may have to filter their urine for several days after ESWL in order to obtain a satisfactory sample size for IRS. The technique described in this report, combining SEM with IRS, requires a solitary urine specimen taken immediately after ESWL, which is convenient for both patient and doctor. In conclusion, consistent stone diagnosis is possible after piezo-

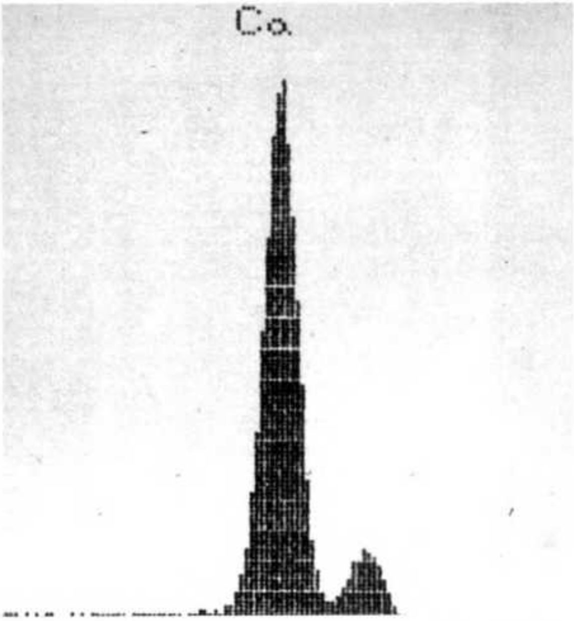

Fig. 5 X-ray emission spectroscopy traces from calcium oxalate.

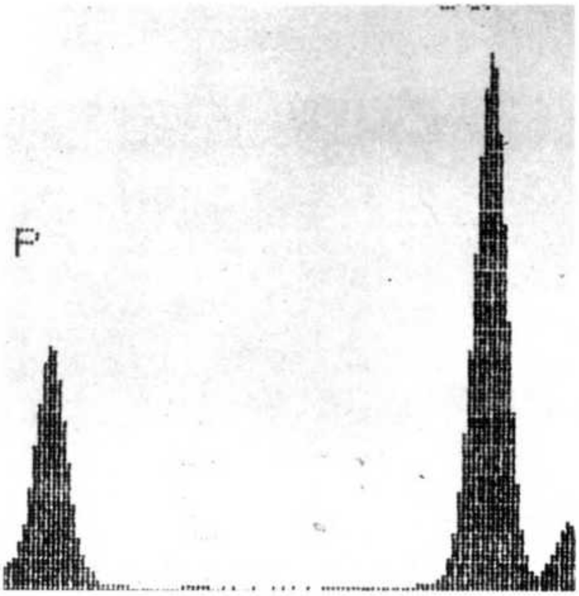

Fig. 6 X-ray emission spectroscopy traces from calcium carbapatite.

electric ESWL. SEM combined with XES is as reliable as IRS as a technique for stone diagnosis. When SEM and XES are available, urine collection should be routine after piezoelectric ESWL and filtration for fragments should be abandoned.

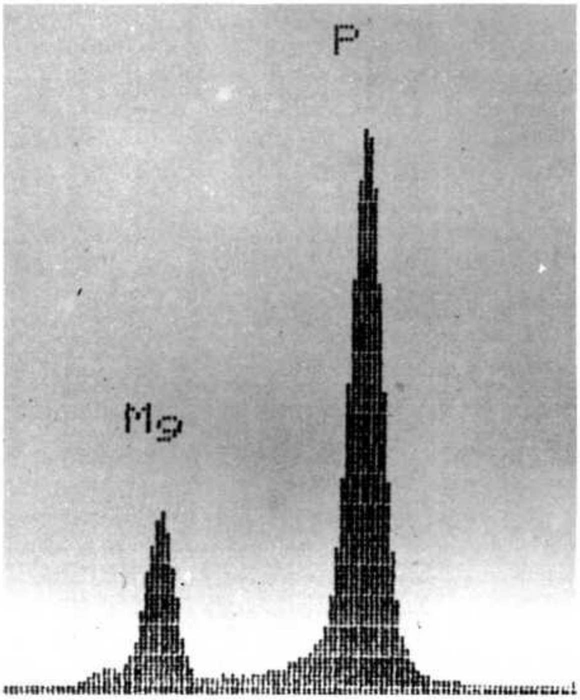

Fig. 7 X-ray emission spectroscopy traces from triple phosphate.

Table Results

Patient No.	*SEM+XES*	*IRS*
1	Calcium carbapatite	Calcium carbapatite
2	Calcium carbapatite	Calcium carbapatite
3	Calcium oxalate ? some calcium Carbapatite	Calcium oxalate Trace of calcium Carbapatite
4	Calcium carbapatite	Calcium carbapatite
5	Calcium carbapatite	Calcium carbapatite
6	Calcium oxalate and trace of calcium apatite	Calcium oxalate
7	Calcium oxalate	Calcium oxalate
8	Calcium oxalate and trace of calcium apatite	Calcium oxalate and some calcium carboxyapatite
9	Ammonium magnesium Phosphate and calcium carbapatite	Ammonium magnesium Phosphate and calcium carbapatite
10	Calcium oxalate	Calcium oxalate
11	Calcium oxalate	Calcium oxalate and trace of calcium carbapatite

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Treatment of Lymphocele Associated with Renal Transplant

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Summary—A new method of operative drainage of lymphoceles following renal transplantation is described. The technique involves intraperitoneal marsupialisation of the lymphocele cavity followed by insertion of a Tenckhoff peritoneal dialysis catheter to splint open the peritoneal window and act as an internal drain.

Lymphocele development is a well recognised complication of renal transplantation, with incidence rates up to 16% (Lerut *et al.*, 1980). The majority of lymphoceles are small and asymptomatic and their management is straightforward. It is the treatment of the rarer large and symptomatic lymphocele which is often difficult. Conservative measures include single or multiple percutaneous needle aspiration (Meyers *et al.*, 1977; Lerut *et al.*, 1980), injection of ^{198}gold colloid into the lymphatic cavity (Williams and Howard, 1981) and instillation of povidone iodine (Teruel *et al.*, 1983). Surgical exploration is indicated if these conservative measures fail and the method advocated by most surgeons is intraperitoneal drainage by marsupialisation (Byron *et al.*, 1966; Ngheim *et al.*, 1982; Rubay *et al.*, 1983; Sollinger *et al.*, 1983; Greenberg *et al.*, 1985). One disadvantage of this technique is that the peritoneal window tends to seal itself very quickly. This may result in failure of the technique and the need for further surgery. This report describes a simple modification of the intraperitoneal marsupialisation technique in which a single cuffed Tenckhoff CAPD catheter is used to maintain the patency of the peritoneal window.

Method

The transplant wound is reopened under general anaesthesia and the lymphocele cavity identified. Any loculi are broken down by digital dissection, taking care to avoid damaging the blood supply and ureter of the transplant. The general peritoneal cavity is opened by a separate short infra-umbilical midline incision. A window is created in the peritoneum separating the lymphocele and peritoneal cavities. The edges of the window are oversewn using a continuous chromic catgut suture. A single cuffed Tenckhoff catheter is then placed in the lymphocele cavity by passing it through the midline incision and then the peritoneal window. The position of the catheter is adjusted so that drainage holes are present on both sides of the peritoneal window (Fig.). The peritoneum in relation to the midline incision is carefully closed with chromic catgut, ensuring that a water-tight seal is achieved. The dacron cuff of the Tenckhoff catheter is sutured to the peritoneum as it is closed. The catheter is then tunnelled subcutaneously to emerge through the skin in a lateral position at the level of the umbilicus. Both wounds are closed with mass nylon

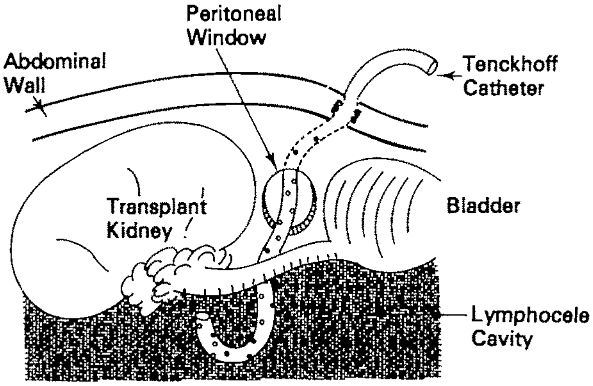

Fig. Lymphocele drainage.

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(no. 1) and a suitable skin suture. The catheter is capped off immediately so that lymph drains through the window into the general peritoneal cavity and not externally. Regular ultrasound scanning can be used to confirm that lymph is not re-accumulating. The Tenckhoff catheter is removed after 3 months.

Discussion

Large symptomatic lymphoceles following renal transplantation are usually difficult to treat. Repeated external percutaneous drainage is the simplest form of management but is potentially dangerous because of the risk of infection. Furthermore, this method requires prolonged bed rest in hospital (Lerut *et al.*, 1980). Internal drainage by marsupialisation has been advocated but we have found that the peritoneal window tends to close quite quickly and this may lead to recurrence of the lymphocele. This problem may be avoided by using an internal stent and the Tenckhoff chronic peritoneal dialysis catheter has all of the necessary design features for this purpose.

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Minimally Invasive Treatment of Ureteric Calculi Using Modern Techniques

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Summary—Between July 1985 and July 1986, 226 upper and 62 distal ureteric calculi were treated. *In situ* extracorporeal shockwave lithotripsy (ESWL) is the treatment of choice for upper and distal ureteric calculi, with success rates of 81 and 76% respectively. Retrograde manipulation of the calculus was undertaken only when *in situ* ESWL was impossible because of difficulty in localisation. Although ESWL after successful mobilisation was successful in 95% of patients, retrograde mobilisation was possible in only 80%. Antegrade ureterorenoscopy via a percutaneous nephrostomy was performed to avoid open surgery if retrograde mobilisation was not feasible, and was successful in 90%. Two second generation lithotripters, the modified Dornier HM3+ and the Wolf Piezolith 2200, both suitable for treatment without anaesthesia, were compared in terms of efficacy. *In situ* ESWL of upper ureteric calculi was successful in 70.6% with the HM3+ and 37.2% with the Piezolith 2200. *In situ* ESWL of middle ureteric calculi was successful in 81.8% with the modified HM3+, while *in situ* treatment of middle ureteric calculi was impossible with the Piezolith 2200 because of inadequate ultrasound localisation. Distal ureteric calculi were treated successfully in 71.4% with the modified Dornier HM3+ and in 64% with the Piezolith 2200. We report our experience of ESWL using the prone position for iliac ureteric calculi; 8 of 10 patients were treated successfully *in situ.*

Since the introduction of ESWL for the treatment of urolithiasis, the incidence of stones in the urinary tract has altered; as the number of renal calculi has decreased, the number of ureteric calculi has increased (Alken *et al.*, 1985).

There are 5 procedures for treating ureteric stones: *in situ* ESWL, ESWL after dislodgement of the calculus into the renal pelvis (UC and ESWL), retrograde ureterorenoscopy (URS), antegrade ureterorenoscopy and ureteric lithotomy.

ESWL has gained acceptance as the main procedure, but debate continues on the respective merits of *in situ* treatment or ESWL after retrograde manipulation.

Owing to the poor initial results of *in situ* ESWL, some authors prefer primary mobilisation of the stone into the renal pelvis (Chaussy and Fuchs, 1985; Miller *et al.*, 1985). Investigations have shown the value of an expansion chamber, formed by surrounding fluids, which facilitates stone disintegration. Conversely, impaction of the stone reduces the shockwave energy and contributes to the failure of *in situ* treatment (Müller *et al.*, 1985). However, only 80% of upper ureteric calculi can be mobilised using ureteric catheters or ureteroscopes. These procedures are more invasive and carry the risk of septicaemia and ureteric perforation, followed by fibrosis and stricture. In addition, the procedures are painful and require epidural or general anaesthesia, particularly in male patients (Rassweiler *et al.*, 1986b; Schmidt *et al.*, 1987).

With the introduction of second generation lithotripters which require no anaesthesia, this situation has to be reviewed again.

Patients and Methods

Procedures can vary according to the localisation of the calculus within the ureter, and the following definitions have been used:

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The *upper ureter* extends from the pelviureteric junction to the transverse process of the third lumbar vertebra.

The *middle ureter* is the area below the third lumbar vertebra to the os sacrum.

The area below the bony pelvis to the ureterovesical junction is defined as the *lower distal ureter.*

For evaluation of the data and comparison of different treatments the following definition of success has been used:

Successful in situ ESWL means complete disintegration of the stone into fragments <2 mm in diameter after 1 or 2 sessions without the need for auxiliary measures due to incomplete fragmentation.

Successful ESWL after retrograde manipulation (ESWL and UC) means successful mobilisation and complete disintegration in 1 or 2 sessions without further auxiliary measures due to incomplete fragmentation.

Selection of patients

The investigation was divided into three parts.

(1) Within a 1-year period (July 1985 to July 1986) 188 upper middle and 96 lower ureteric calculi were treated at Katharinenhospital and revealed a varying approach to upper and distal ureteric calculi. All ESWL procedures were performed with the standard Dornier HM3 lithotripter (14 cm ellipsoid, 80 nF generator).

(2) From January 1987 to July 1987 a prospective study was performed to compare the modified HM3 lithotripter (17 cm ellipsoid, 40 nF generator) installed at the Katharinenhospital, Stuttgart, with the Piezolith 2200 installed at the Kreiskrankenhaus, Kempten, in terms of efficacy of *in situ* ESWL for upper, middle and distal ureteric calculi. The procedures involved the use of anaesthesia. The technical data are listed in Table 1.

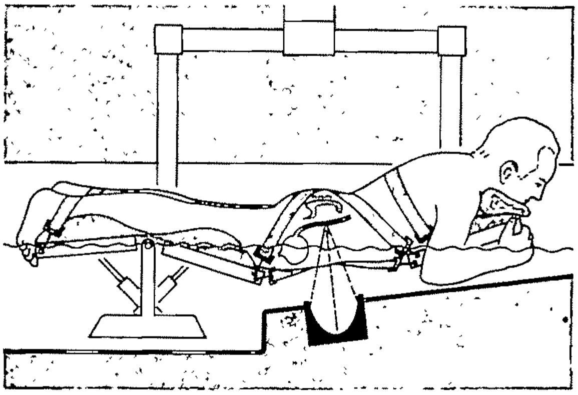

Fig. 1 Prone position for ESWL for presacral ureteric calculi.

A total of 66 upper, 22 middle and 14 distal ureteric calculi were treated in Stuttgart and 43 upper, 19 middle and 25 lower ureteric stones in Kempten.

(3) In August, *in situ* ESWL in the prone position for middle ureteric calculi, superposed by the os sacrum, was used for the first time in Stuttgart (modified HM3). Until November 1987 the first 10 patients were treated in this way (Fig. 1).

According to the general concept of minimal invasiveness and morbidity (Eisenberger and Miller, 1987), the following approach was used at both centres. *In situ* ESWL was the treatment of choice for upper ureteric calculi (Fig. 2). Retrograde mobilisation was used only when the stone was difficult to locate (because of skeletal deformity, stones close to the vertebral column, gross obesity, or in emergency cases, *i.e.* hydronephrosis, septicaemia) or after failure of *in situ* ESWL.

If retrograde dislodgement was impossible—even using the ureteroscope—antegrade ureteroscopy was performed via a nephrostomy tract to avoid open surgery.

Until August 1987 all middle ureteric calculi were initially manipulated. If retrograde mobilisa-

Table 1 Technical Data

	HM3+	*Piezolith 2200*
Shockwave generation	Underwater electrode	Piezoceramic elements
Focussing	Semi-ellipsoid	Spheric alignment
Aperture	17 cm	30 cm
Shockwave coupling	Complete waterbath	Partial waterbath
Stone localisation	2 undercouch X-ray tubes	Coaxial ultrasound
Stone monitoring	Intermittent	Permanent
Peak pressure	950 bar	1100 bar
Focal size	50 × 30 mm	11 × 3 mm

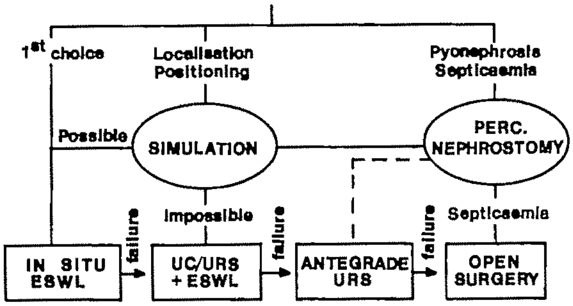

Fig. 2 Approach to upper ureteric calculi (Katharinen Hospital, Stuttgart).

tion failed, the stones were removed under ureteroscopic vision using forceps, the Dormia basket or ultrasound lithotripsy.

In August 1987, middle ureteric calculi were treated using *in situ* ESWL in the prone position. When location was difficult, contrast dye was applied intravenously or via a nephrostomy tube. After failure of *in situ* ESWL, retrograde dislodgement was performed.

Since February 1987, *in situ* ESWL has been the treatment of choice for lower ureteric calculi. If it failed, the calculus was retrieved with the Zeiss loop or with the ureteroscope. Ureteric lithotomy was the final option (Fig. 3).

All patients treated with the standard HM3 lithotripter received anaesthesia (90% epidural, 10% general).

After modifications to the HM3 lithotripter (40 nF Generator vs. 80 nF Generator, 17 cm ellipsoid vs. 14 cm ellipsoid), which reduced pain, analgesic requirements were changed.

Ten minutes before commencing ESWL, 100 mg tramadole (Tramal) were injected. If the patient complained of pain, 50–100 mg tramadole were added, and in cases of anxiety 5–10 mg midazolam (Dormicum) were administered. If pain was intolerable, 100–200 mg ketamine were administered intravenously.

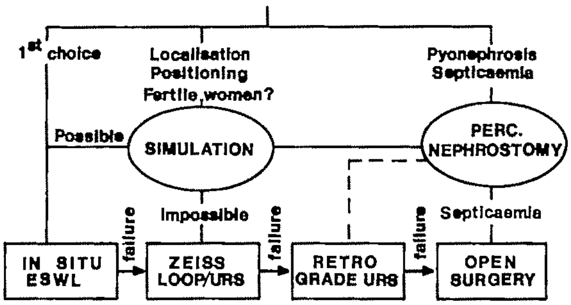

Fig. 3 Approach to distal ureteric calculi (Katharinen Hospital, Stuttgart).

With the Piezolith 2200 no basic analgesia was used. If pain was experienced during the procedure, local anaesthesia was used.

Results

July 1985 to July 1986 (Standard HM3 lithotripter)

A total of 269 therapeutic procedures were carried out on 224 patients with upper and middle ureteric calculi. Most patients were treated with *in situ* ESWL (n = 162) with an overall success rate of 81% (131 patients), including 8% successful secondary *in situ* ESWL procedures.

A total of 68 patients underwent ESWL after retrograde mobilisation of the calculus, with successful dislodgement and disintegration in 54 patients (79%). Antegrade ureterorenoscopy was successful in 19 or 21 patients (90%). Retrograde ureterorenoscopy was less effective, with a success rate of 44% (16 patients). Open surgery was necessary in only 2 instances: in 1 patient a scarred stenosis after prior surgery required ureteric lithotomy and the other patient underwent nephrectomy due to persistent septicaemia after failure of conservative treatment.

A comparison of the efficacy of *in situ* ESWL and shockwave lithotripsy after retrograde mobilisation showed no statistically significant difference with respect to success rates and length of hospital stay. Due to attenuation of shockwave energy, a higher number of shockwaves and an increased generator voltage was necessary for successful *in situ* treatment; since it was a less invasive procedure, the overall rate of complications was significantly lower (Table 2).

To evaluate the factors involved in failure of *in situ* ESWL the data were classified according to stone size and degree of obstruction.

In the treatment of calculi < 1 cm in diameter, *in situ* ESWL was successful in 89 of 102 cases (87%)

Table 2 *In situ* ESWL versus UC and ESWL for Upper and Middle Ureteric Calculi

	In situ ESWL (N=162)	*UC+ESWL (N=68)*
Success rate	81%	79%
Shockwaves	1536	1095
Final generator voltage	21 kV	18 kV
Hospital stay (days)	5	5
Complications (septicaemia, perforation, stenosis)	5.6%	15%

and ESWL after retrograde manipulation (ESWL and UC) in 40 of 52 cases (77%). For calculi between 1 and 2 cm in diameter, *in situ* ESWL was successful in 35 of 54 patients (65%), ESWL and UC in 11 of 15 patients (73%).

For calculi > 2 cm in diameter, both *in situ* ESWL (n = 6) and ESWL and UC (n = 1) were successful in all cases. There was no statistically significant difference between the success rates of each procedure.

Calculi causing incomplete obstruction were treated successfully with *in situ* ESWL in 99 of 118 cases (84%), with ESWL and UC in 35 of 42 cases (85%).

Stones causing complete obstruction with dilatation of the upper renal tract (expansion chamber effect) were treated successfully with *in situ* ESWL in 14 of 19 patients (74%), using ESWL and UC in 7 of 10 patients (70%). There was no statistically significant difference between the success rates of each procedure. For impacted ureteric calculi, *in situ* ESWL was successful in 18 of 25 cases (72%), while ESWL and UC was successful in 13 of 14 cases (93%) ($P < 0.05$).

ESWL for lower ureteric calculi

The distribution and success rates of 122 therapeutic procedures in 96 patients with lower ureteric stones are listed in Table 3.

Modified HM3 (HM3+) versus Piezolith 2200

With the modified HM3, 48 of 68 upper (70.6%), 18 of 22 middle (81.8%) and 10 of 14 pelvic ureteric calculi (71.4%) were treated successfully *in situ*. Following the failure of *in situ* treatment, retrograde mobilisation followed by ESWL was necessary in 24 patients with upper and middle ureteric calculi and was successful in all cases. After failure of *in situ* ESWL for distal ureteric calculi the calculi were removed with either the Zeiss loop (n = 3) or the ureteroscope (n = 1).

Using the Piezolith 2200, 16 of 43 upper (37.2%) and 16 of 25 distal ureteric calculi (64%) were treated successfully *in situ*; this treatment failed in all cases with middle ureteric calculi (n = 18).

Table 3 Treatment of Lower Ureteric Calculi (July 1985–July 1986)

		Success	
	No.	*No.*	*%*
In situ ESWL	28	22	77
Zeiss loop	63	42	67
Retrograde URS	30	28	93
Open surgery	1	1	1

After the failure of *in situ* ESWL with the Piezolith 2200 for upper and middle ureteric calculi, ESWL after retrograde dislodgement of the calculus was used in 45 cases. Stone mobilisation using ureteric stents succeeded in 37 cases and the ureteroscope was required in 8. All of the mobilised calculi were disintegrated afterwards using ESWL. After the failure of *in situ* ESWL of distal ureteric stones, removal with the Zeiss loop was performed in 6 cases; in 3 cases ureteroscopic stone removal was necessary.

Comparison of the treatment data (Table 4) shows significant differences in the number of shockwaves (1997 vs. 2855) and of multiple ESWL treatments (15 vs. 45%) between the HM3+ and the Piezolith 2200.

Intravenous analgesia was used in 72% of *in situ* ESWL procedures (n = 25) with the HM3+; 20% of patients (n = 21) required i.v. analgesia and sedation; 6 received general anaesthesia and only 2 required no analgesia.

With the Piezolith 2200 all *in situ* treatments were performed without analgesia.

ESWL of middle ureteric calculi (prone position)

In situ ESWL of middle ureteric calculi superposed by the os sacrum in the prone position was performed successfully in 8 of 10 patients; 2 stones were dislodged into the renal pelvis and disintegrated using shockwaves.

Stone localisation was easily achieved in 5 cases. In 4 cases contrast dye was administered intra-

Table 4 Modified HM3+ versus Piezolith 2200. Treatment Data

	Mod. HM3+ (n = 104)		*Piezolith 2200 (N = 87)*	
	No.	*%*	*No.*	*%*
No. of shockwaves	1997		2855	
Auxiliary measures before ESWL				
UC	36	35	33	38
URS	10	10	8	9
Nephrostomy	2	2	—	—
Auxiliary measures after ESWL				
Double J	6	6	—	—
Nephrostomy	1	1	—	—
URS	1	1	3	3
Zeiss loop	—	—	8	9
Multiple ESWL procedures	16	15	39	45

venously and in 1 case via a nephrostomy tube inserted 2 days before the procedure because of imminent septicaemia. Complications after ESWL, *e.g.* intestinal disorders, did not occur.

Discussion

In situ ESWL for upper and distal ureteric calculi

Because initially poor results with *in situ* ESWL, with success rates of 50 to 62%, retrograde mobilisation of the calculus into the renal pelvis became a routine procedure in several centres (Algood *et al.*, 1983; Fuchs *et al.*, 1984; Chaussy and Fuchs, 1985; Eisenberger *et al.*, 1985; Meyer *et al.*, 1985; Miller *et al.*, 1985; Müller *et al.*, 1985; Schmidt *et al.*, 1987). The clinical experience and experimental work of Müller *et al.* (1985) revealed factors that contributed to the failure of *in situ* ESWL, such as total obstruction (no passing of contrast dye), stone size >10 mm in longitudinal diameter, and prolonged impaction of the calculus.

Particularly poor results were obtained when *in situ* treatment was used on stones impacted in the ureter with no passage of urine. Thus it was proposed that the main reason for failure was the lack of suitable interphases between urine and the calculus (expansion chamber).

Another reason for the poor results was the proximity of the vertebral column: partial reflection of the shockwave at the transverse processes leads to further attenuation of energy; the superposition of bones on at least 1 X-ray monitor produces distortion, reduces the reliability of stone localisation and limits the use of ultrasound for the detection of ureteric calculi.

To compensate for the attenuation of shockwave energy, higher generator voltage is necessary. For renal calculi an average voltage of 18 kV is sufficient; for ureteric calculi 21 kV were used.

To ensure undisturbed shockwave application and stone localisation we used a special positioning technique. Extreme rotation of the patient not only guarantees an undisturbed pathway for the shockwave, but also a clear view on both X-ray monitors (Fig. 4A). Additional flexion of the patients' leg improves stabilisation in this uncomfortable position (Fig. 4B).

This procedure is limited to calculi which are at least 1 cm lateral to the vertebral column and to relatively slim patients, since the distance from skin to stone increases with rotation (Fig. 5). In these cases we recommend trial positioning the day before treatment to establish whether or not it is feasible.

Because liquid interphases are of major importance for optimal shockwave coupling, we recommend excentric (cranial) focussing, starting with shockwave exposure of the upper part of the stone which is surrounded by urine. After partial disintegration the caudal parts can be treated (Rassweiler *et al.*, 1986a and b; Eisenberger and Miller, 1987). In some circumstances, such as obesity, stones close to the spine and skeletal deformity, retrograde manipulation of the stone was inevitable. Although successful disintegration of the stone within the renal pelvis was achieved in 95% of cases, retrograde mobilisation succeeded in only 80%. Thus a total success rate of 79% was noted after retrograde dislodgement, which is similar to the success rate of *in situ* ESWL.

On the other hand, *in situ* ESWL was followed by fewer complications. It is less invasive and has gained increasing acceptance in the treatment of distal ureteric stones.

We recommend that the patient be supine for shockwave application via the gluteal region. This is easily achieved as the X-ray monitors show an a.p. view (Fig. 6A) (Rassweiler *et al.*, 1986a; Eisenberger and Miller, 1987). Other centres prefer a sitting position for shockwave application via the birth channel (Fig. 6B) (Miller *et al.*, 1986).

Fertile women were excluded from *in situ* ESWL for distal ureteric calculi to avoid shockwave damage to the ovaries. Experimental investigations, however, have revealed no mutagenic effect from shockwaves (Carrol and Shi, 1986).

The middle ureter superposed by the pelvic bones, is generally considered unsuitable for *in situ* ESWL treatment, since exact positioning of the stone within the second focus is almost impossible if the patient is supine. According to Jenkins (1986), ESWL in the prone position provides a solution to this problem, providing unreflected shockwave application.

Although absorption of shockwave energy by air-filled intestines leading to intestinal haemorrhage, was seen in animal experiments (Eisenberger *et al.*, 1977), no complications were encountered by Kuo (1988) and Tiselius and Andersson (1988).

Modified HM3 versus Piezolith 2200 for in situ ESWL of upper and distal ureteric calculi

The success of the Dornier HM3 lithotripter has led to the development of second generation lithotripters which combine the efficacy of the HM3 with reduced invasiveness and easier handling, in particular pain-free treatment.

The Piezolith 2200 is a second generation

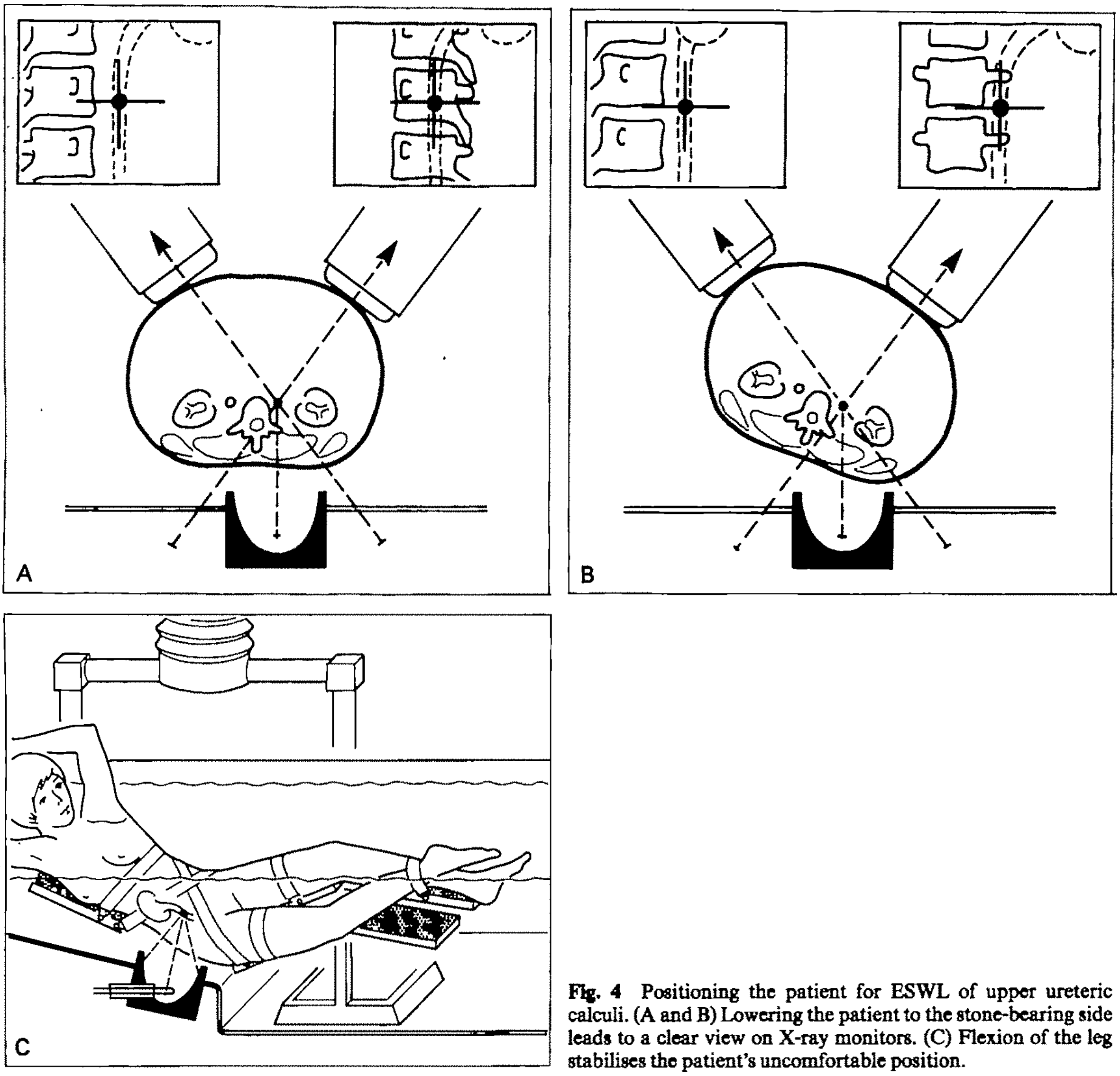

Fig. 4 Positioning the patient for ESWL of upper ureteric calculi. (A and B) Lowering the patient to the stone-bearing side leads to a clear view on X-ray monitors. (C) Flexion of the leg stabilises the patient's uncomfortable position.

lithotripter which uses piezoelectric elements for shockwave generation. The special alignment of more than 1000 piezoelectric elements provides a high pressure peak of 1100 bar within a focal area of 3 × 11 mm.

The most important parameters of pain during shockwave application are the quantity of the applied energy and its geometrical distribution. Enlargement of the aperture of the shockwave focussing system concentrates the energy within a smaller area. This permits reduction of the applied energy and reduces the pressure exposure of the skin at the shockwave entry (Schmidt *et al.*, 1987). Modifications to the standard HM3 lithotripter were therefore introduced. A new shockwave generator with reduced capacity (40 versus 80 nF) was installed to achieve reduced pressure peaks at corresponding voltage. An enlarged ellipsoid (17 versus 14 cm) reduced the focal area (50 × 13 mm versus 90 × 15 mm).

These modifications have led to less painful ESWL, where analgesic medication replaces general or epidural anaesthesia without affecting the efficacy of stone disintegration (Graff *et al.*, 1987; Schmidt *et al.*, 1987).

Completely pain-free ESWL, however, requires larger apertures of the focussing system. ESWL using the Piezolith 2200 with an aperture of 30 cm

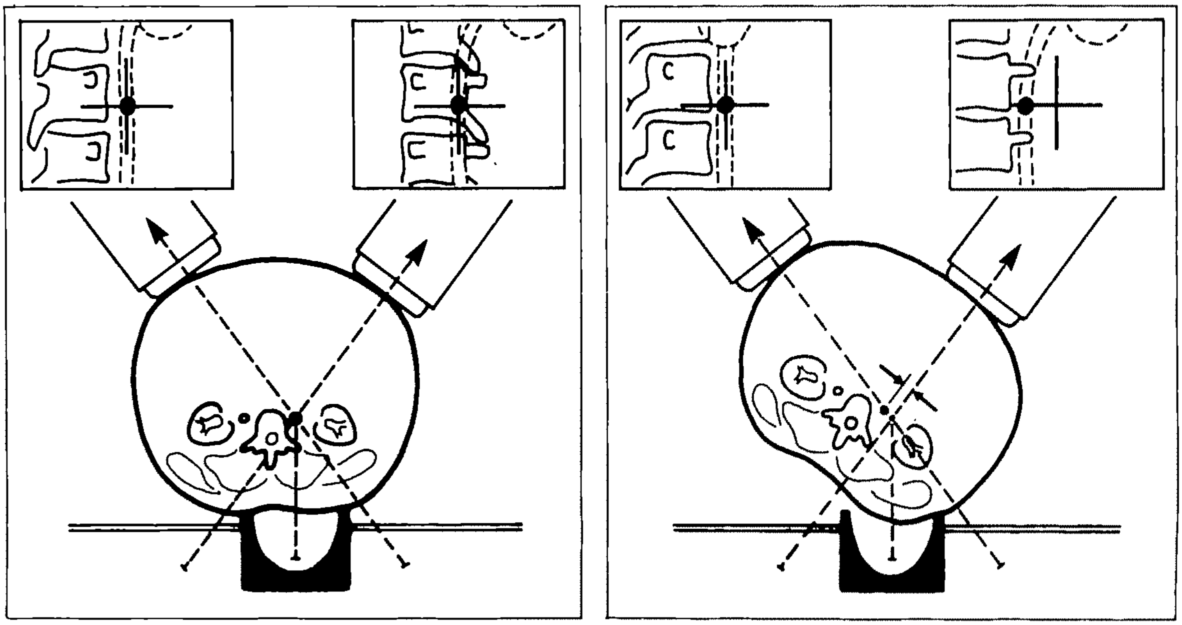

Fig. 5 Problems of positioning for ESWL of upper ureteric calculi in obese patients. Lowering the stone-bearing side increases the distance from skin to stone.

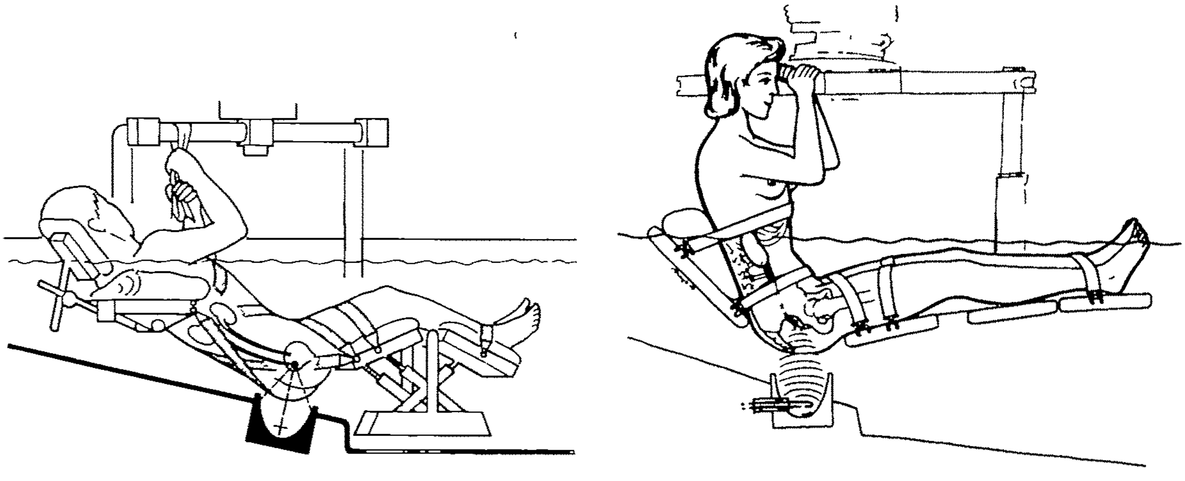

Fig. 6 Positioning for ESWL of distal ureteric calculi. (A) Shockwave application via the gluteal region. (B) Shockwave application via the birth channel.

requires no analgesic medication at all (Ziegler *et al.*, 1986). Focussing systems of that size are compatible with ultrasound localisation systems only, since the larger reflector superimposes the stone on X-ray monitors. Ultrasound, however, allows detection of ureteric stones only in the dilated upper parts of the ureter or within the intramural part of the distal ureter. All other stones have to be dislodged into the renal pelvis or removed using the loop or ureteroscope. Any reduction in shockwave energy, which is necessary for pain reduction, reduces the success of *in situ* treatment. The use of ultrasound for stone localisation, which is mandatory for pain-free shockwave treatment, limits the indications for *in situ* ESWL to a small percentage of ureteric calculi.

The modified HM3 represents a reasonable compromise, combining *in situ* treatment of ureteric calculi with less painful ESWL which can be performed without invasive anaesthesia.

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Ultrasound Cystography in the Diagnosis of Vesicoureteric Reflux

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Summary—Vesicoureteric reflux is common in children with urinary tract infection and may cause end-stage renal failure. The diagnosis is usually based on micturating cystourethrography (MCU). We describe an alternative technique using ultrasound during bladder infusion with agitated saline. Comparison of the 2 methods shows ultrasound to be 100% sensitive in the detection of grades 3 and 4 reflux. Conclusive evidence of reflux was seen in 2 cases where MCU was subsequently normal, questioning the role of MCU as the gold standard.

Vesicoureteric reflux (reflux) is found in 20 to 30% of children investigated for proven urinary infection (White, 1987). Renal scarring, or reflux nephropathy, is caused by the combination of intrarenal reflux and urinary infection (Ransley and Risdon, 1981). In children and young adults this scarring is responsible for 30% of cases of hypertension and 20% of patients presenting with end-stage renal failure (Smellie, 1980). The diagnosis currently depends on micturating cystourethrography, which is an invasive and unpleasant investigation quite unsuitable for screening. Consequently, babies and children are investigated only following a urinary tract infection when renal damage may already have occurred.

Ultrasound is an attractive imaging technique which is non-invasive, involves no ionising radiation and is usually well tolerated by the young. The effectiveness of ultrasound in the diagnosis of reflux has so far been limited (Tremewen *et al.*, 1976). Reflux is an intermittent phenomenon and unless there is parenchymal scarring, the renal tract in affected patients may appear sonographically normal.

Ultrasound cystography has been suggested as a possible alternative to standard MCU for the detection of reflux. We describe our technique and the results of a prospective study comparing ultrasound cystography and standard MCU in children with urinary tract infections.

Patients and Methods

Seventy patients, aged 1 month to 27 years (mean 7 years), with a proven urinary tract infection were investigated by ultrasound cystography and a standard MCU.

Preliminary renal tract ultrasound was performed using a 5 MHz mechanical sector scanner (Siemens Sonoline SX). Particular attention was paid to the detection of ureters behind the bladder, pelvicaliceal distension and the degree of bladder fullness. All scans were performed by 1 of 3 ultrasonographers.

The child was catheterised and the bladder emptied. The bladder was then filled by drip infusion with 0.9% saline, which had previously been shaken within its container to produce a suspension of air microbubbles. The kidneys and bladder were scanned in longitudinal and transverse planes during filling and any changes noted. The bladder was filled to the point of a reflex void in an infant, or the feeling of fullness in an older child.

Reflux was graded according to the Report of the International Reflux Study Committee (1981). Lower ureteric reflux (grade 1 or 2) was suggested by the appearance of an anechoic tubular structure behind the bladder seen in 2 planes. Pelvicaliceal

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Based on a Poster Demonstration at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

Table Comparison of Ultrasound "Bubble" Cystography and Micturating Cystourethrography in 133 Ureters

Result of bubble cystogram	*Result of micturating cystourethrography*			
	Abnormal	*Normal*	*Total*	
Abnormal	18	11	29	Positive predictive value = 62% (18/29)
Normal	9	95	104	Negative predictive value = 91% (95/104)
Total	27 Sensitivity 67% (18/27)	106 Specificity 90% (95/106)		

dilatation or the presence of microbubbles in the renal pelvis was taken as evidence of grade 3 reflux or greater. Ultrasound examination during voiding was not performed. The bladder was then emptied via the catheter and the child proceeded immediately to a standard MCU. This was performed by the same experienced uroradiological team on all occasions and the reflux graded as above.

Results

Of the 70 patients studied, 2 refused catheterisation and took no further part in the study. One was too unco-operative for ultrasound, although micturating cystourethrography was possible. Another co-operated for ultrasound examination of 1 side only; 133 ureters were available for assessment.

The results of the 2 techniques are given in the Table. MCU has been used as the "gold standard" for the calculation of sensitivity, specificity and predictive values. A total of 27 ureters were found to be refluxing (1 grade 4, 13 grade 3, 5 grade 2 and 8 grade 1). There were 9 false negative results, but in 8 of these reflux only occurred during voiding (6 grade 1 and 2 grade 2).

There were 11 positive findings on ultrasound where MCU was normal. In 5 cases there were lower ureteric changes only; the other 6 had pelvicaliceal distension. In 2 of these, microbubbles were clearly seen within the affected renal pelvis (Figs 1–3).

Ultrasound changes were seen in all cases of grades 3 and 4 reflux but only 3/5 (60%) of grade 2 and 2/8 (25%) of grade 1.

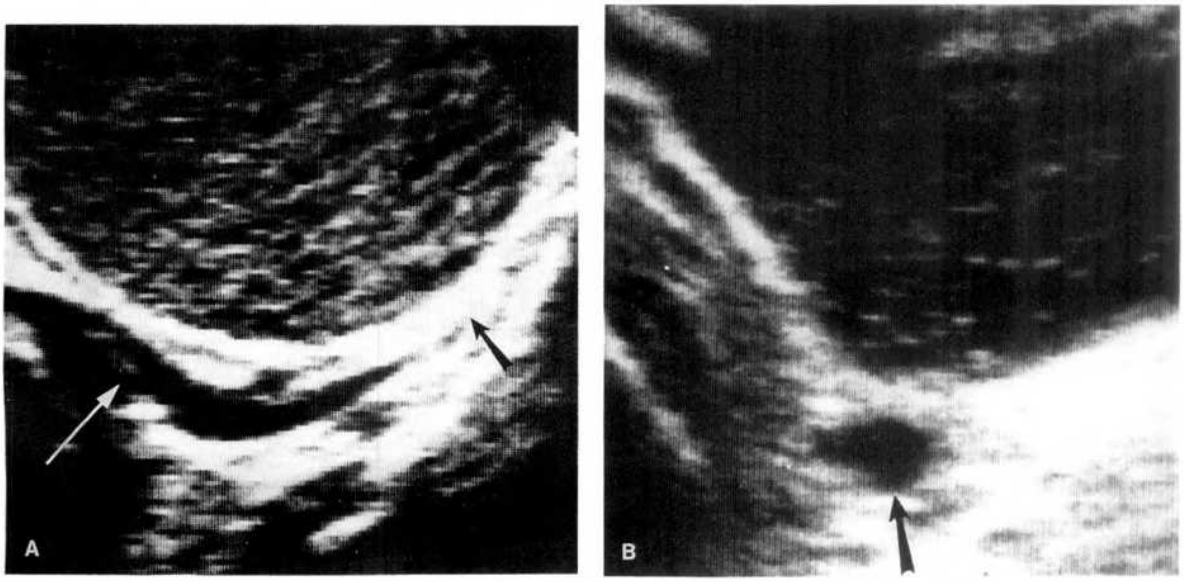

Fig. 1 (A) Oblique section of bladder containing microbubbles. The ureter (white arrow) and vesicoureteric junction (black arrow) are seen behind it. (B) Transverse section of bladder and ureter (arrow).

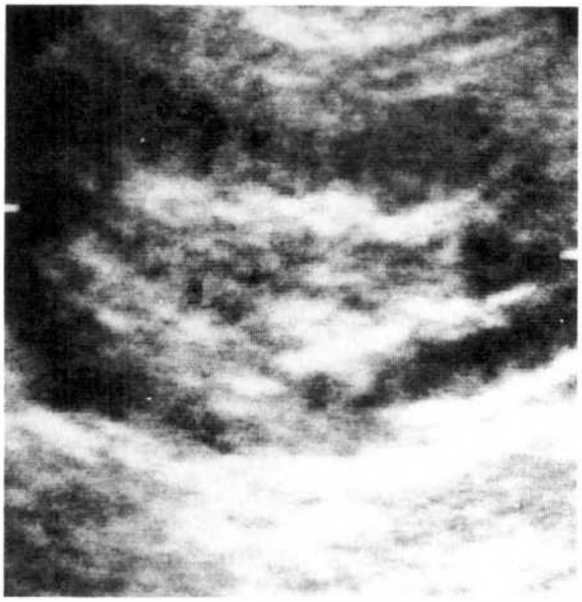

Fig. 2 An apparently normal kidney on preliminary ultrasound.

Discussion

We have shown that ultrasound cystography can reliably detect changes of grade 3 reflux or greater; this is in agreement with the work of Kessler and Altman (1982) and Schneider *et al.* (1984).

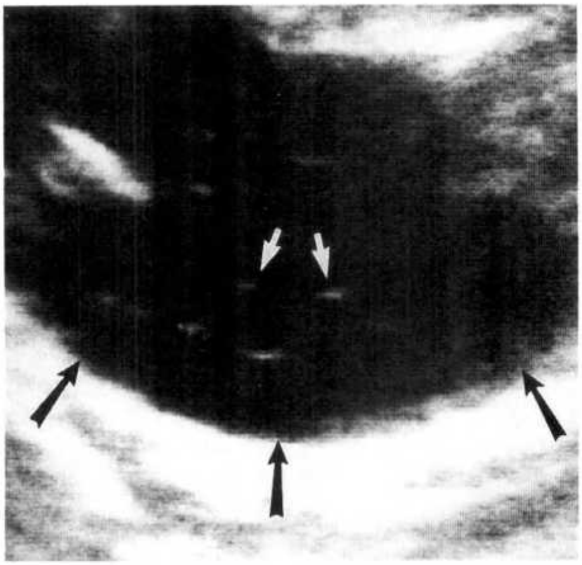

Fig. 3 Same kidney as in Figure 2 after bladder filling (arrowheads). The pelvicaliceal system is dilated (black arrows) and contains microbubbles (white arrows), indicating grade 3 reflux. MCU showed grade 2 reflux only.

Our high rate of false positive results was disappointing. These were all girls examined in the early part of the series and it seems likely that the ovaries were falsely identified as ureters during bladder filling. Ovaries may not have been demonstrated on the preliminary scan due to a small bladder volume, but subsequently became visible as the bladder filled. This error was corrected later in the study by using stricter criteria; a refluxing ureter was only so-called when a tubular structure was seen in longitudinal and transverse planes.

A significant disadvantage of our protocol is that the renal tract is not examined during voiding. Consequently, in all 8 cases where reflux occurred only on voiding, ultrasound cystography was normal. However, it is a matter of debate whether these grades of reflux are of clinical significance.

One of the major advantages of the technique is the absence of ionizing radiation. This enables screening of kidneys and ureters throughout bladder filling, rather than the brief glimpses practised with fluoroscopy during a standard MCU. This may help to explain the finding of definite pelviureteric dilatation in 6 cases where MCU was subsequently normal. One of these MCU negative/"bubble" cystogram positive cases is demonstrated in Figures 4–6. An intravenous urogram performed 8 weeks before had shown caliceal clubbing and cortical scarring, thereby making the diagnosis of reflux nephropathy. It is quite possible that these 6 "false" positives are really "true" positives, which draws into question the use of the MCU as the gold standard. There is certainly some evidence from radionuclide studies to suggest that reflux occurs in children with a negative MCU (Chapman *et al.*, 1988). If this did happen in our patients, it would have given ultrasound cystography a sensitivity of 89% (24/27) with a positive predictive value of 83% (24/29).

Our results show that ultrasound "bubble cystog-

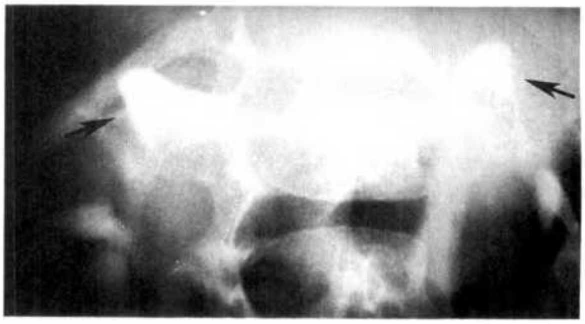

Fig. 4 IVU showing distorted upper calices (arrows), suggesting reflux nephropathy.

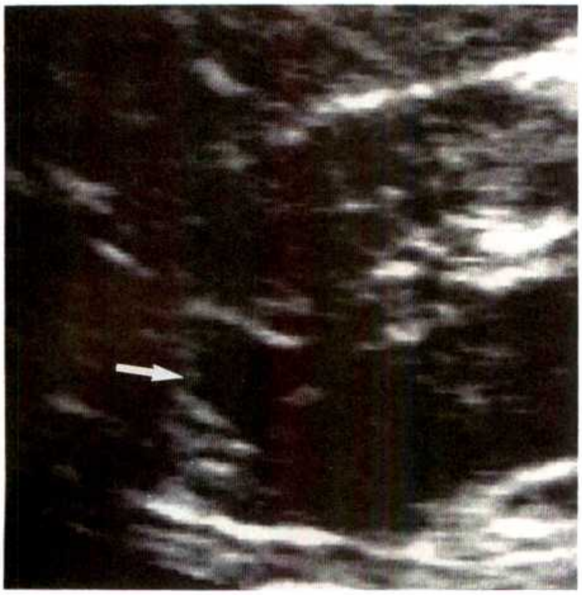

Fig. 5 Preliminary ultrasound of right kidney in same patient showing clubbed upper pole calix (arrow).

raphy" is a useful technique for detecting changes of reflux during bladder filling, but misses mild grades occurring only during voiding. Pelvicaliceal and ureteric dilatation were the main criteria for diagnosing reflux. However, in those cases where MCU was subsequently normal, the presence of microbubbles within the renal pelvis provided conclusive evidence that reflux had occurred. If increasing dilatation during bladder filling or micturition is accepted as sole evidence of reflux, microbubbles would not be needed. Theoretically a technique could then be devised to detect reflux during normal voiding. This would avoid the need for catheterisation, the most unpleasant aspect of both methods. We propose that this technique should be considered as an alternative to MCU in the detection of reflux.

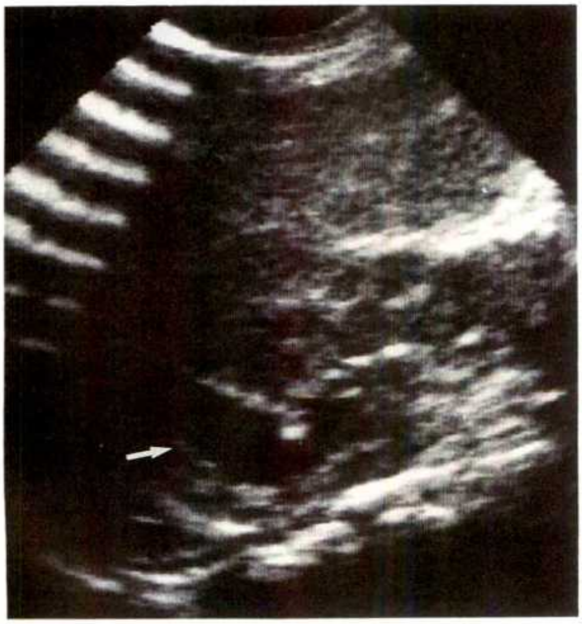

Fig. 6 Pelvicaliceal distension (arrow) in the same kidney as in Figure 5 during bladder filling, indicating reflux.

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Malignant Lymphoma of the Lower Urinary Tract

A Clinicopathological Study with Review of the Literature

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Summary—The clinical and histopathological findings are reported in 3 primary malignant lymphomas of the lower urinary tract. Two arose in the bladders of a 70-year-old man and a 67-year-old woman. The first was histologically low grade and the patient remains free of disease after more than 7 years. The second was an intermediate grade neoplasm and the patient died after 39 months. The third tumour was found in the urethra of a 76-year-old woman and it appears to represent only the third primary malignant lymphoma described at this site. The bladder is an uncommon primary site of extranodal lymphoma. Most patients present with haematuria and cystoscopy shows 1 or more solid, round, tumour-like masses. Histological grade, particularly follicle formation, appears to have predictive value.

Malignant lymphomas involve the lower urinary tract in up to 13% of patients with advanced disease (Sufrin *et al.*, 1977), but primary lymphomas rarely arise at this site. Since the first description by Eve (1885), isolated reports have appeared from time to time, the largest series being that of Bhansali and Cameron (1960), who presented 8 cases and reviewed the literature. A further 34 patients have since been reported (Borski, 1960; Ramioul and Maquinay, 1961; Rosenberg *et al.*, 1961; Parton, 1962; Pontius *et al.*, 1963; Elizade *et al.*, 1965; Stitt and Colapinto, 1966; Lange *et al.*, 1968; Wang *et al.*, 1969; Santino *et al.*, 1970; Freeman *et al.*, 1972; Aquilina and Bugeja, 1974; Makinen *et al.*, 1979; Winter *et al.*, 1979; Pak *et al.*, 1980; Cato, 1981; Mincione, 1982; Forrest *et al.*, 1983; Chaitin *et al.*, 1984; Gohji *et al.*, 1985; Gupta *et al.*, 1985; Heaney *et al.*, 1985; von Bianchi *et al.*, 1985; Aigen and Phillips, 1986; Lewi *et al.*, 1986; de Bruyne *et al.*, 1987; Touhami *et al.*, 1987). This makes a total of 66 cases. The diagnosis is an important one to make because the natural history, prognosis and management of these neoplasms differ from those of the more common carcinomas.

We present 3 new cases of lower urinary tract lymphoma, 2 in the bladder and 1 in the female urethra. We also review the literature in order to document the clinical and pathological features of these tumours, with particular emphasis on various aspects of the histopathological diagnosis.

Patients and Methods

The Histopathology Department of the Exeter Health Authority serves a population of 280,000. Between 1978 and 1987, surgical specimens of the lower urinary tract were received from 715 patients with carcinoma and 7 with sarcoma, compared with 3 specimens (0.4%) in which a diagnosis of primary lymphoma was made. Representative material from each of these 3 patients was fixed in 10% buffered formalin and processed in the usual manner. Sections were stained with haematoxylin and eosin, Gordon and Sweet's reticulin, periodic acid-Schiff and Unna-Pappenheim methyl green pyronin. Permanent sections were also incubated with a panel of commercially available antisera (Table), using appropriate positive and negative controls such as substitution of normal for test sera. All tumours were classified according to the Kiel

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Table Summary of Immunohistochemical Findings

				Case 2		
Markers	*Sources*	*Specificity*	*Case 1*	*Biopsy*	*Autopsy*	*Case 3*
Leukocyte Common Antigen	Dako	Lymphocytes	+++	–	–	+++
MBI	Eurodiagnostics	All B cell and some peripheral T cell lymphomas	+++	–	–	+++
L26	Dako	Most B cell lymphomas	+++	–	N.D.	+++
MTI	Eurodiagnostics	T cell and some B cell lymphomas	±	±	–	±
LI	·U.C.H.	T cell lymphomas	–	–	N.D.	–
Ber-H2	Dako	Reed-Stenberg cells, and some T cell lymphomas	–	–	N.D.	–
IB5	ICRF	HLA DR antigen in most B cell lymphomas	++	±	–	+
Lysozyme	Dako	Phagocytic cells	–	–	±	±
Alpha 1 anti-chymotrypsin	Dako	Phagocytic cells	–	–	N.D.	–
M1	Dako	Granulocytic cells	–	–	N.D.	–
S 100	Dako	Various cells including Langerhans cells	±	–	–	–
Vimentin	Dako	Connective tissue intermediate filament	–	–	–	–
Desmin	Dako	Intermediate filament of muscle	N.D.	–	N.D.	–
CAM 5.2	Becton Dickinson	Cytokeratin 39–50 KD in epithelial cells	–	–	–	–
HMFG 1 and 2	Unipath	Epithelial cell membranes	–	–	–	–
Neuron, Specific Enolase	Dako	Neuroendocrine cells	–	–	N.D.	–
Chromogranin A.	Immunon	Neuroendocrine cells	–	–	N.D.	–

N.D. = not done; – = negative; ± = equivocal; +, ++, +++ = positive with different degrees of strength.
For details of specificity see Mason, D. Y., Gatter, K. C. The role of immunocytochemistry in diagnostic pathology. *J. Clin. Pathol.* 1987; **40**: 1042–1054.

classification (Lennert *et al.*, 1975). Comparable terms from the National Cancer Institute (1982) working formulation are indicated in brackets.

Case Reports

Case 1. A 70-year-old white male first presented with painless haematuria and a small histologically confirmed papillary transitional cell carcinoma was resected from the left wall of the bladder. A recurrence 1 year later was treated by diathermy. Follow-up cystoscopies were normal until 3 years later, when a solid tumour was discovered away from the site of the previous carcinomas. This could not be treated endoscopically and a partial cystectomy was carried out. A round mass 6 cm in diameter was located in the dome of the bladder, the bulk of which appeared to be intramural with only minor involvement of the mucosa. Separate from the main lesion, tumour tissue also surrounded the superior vascular pedicle and a few enlarged lymph nodes were noted nearby. After the diagnosis of lymphoma had been made the patient was reassessed by the Department of Oncology. He gave no history of B symptoms and clinical examination revealed no abnormality. Results of biochemical and haematological investigations (including bone marrow aspirate and trephine biopsy) were normal, but a lymphangiogram demonstrated enlarged iliac, inguinal and pre-aortic lymph nodes, considered to be consistent with infiltration by lymphoma. He received iliac and pelvic irradiation and 7 years later there has been no recurrence.

Microscopic examination of the partial cystectomy specimen showed a malignant lymphoma which infiltrated the full thickness of the bladder wall and extended into surrounding fat. Follicle formation was clearly apparent within the tumour (Fig. 1). The cell population comprised centrocytes (small cleaved follicle centre cells) with a significant admixture of centroblasts (large follicle centre cells) (Fig. 2). Similar tumour was present in the neighbouring lymph nodes. The neoplasm was classified as malignant lymphoma, mixed centrocytic and centroblastic with follicle formation (follicular, mixed small cleaved and large cells) and thus of low grade. Immunohistochemical markers showed a strong positive reaction with Common Leukocyte Antigen, L26 and MB1 with weaker staining for HLA DR. These results indicated a lymphoma of B cell origin.

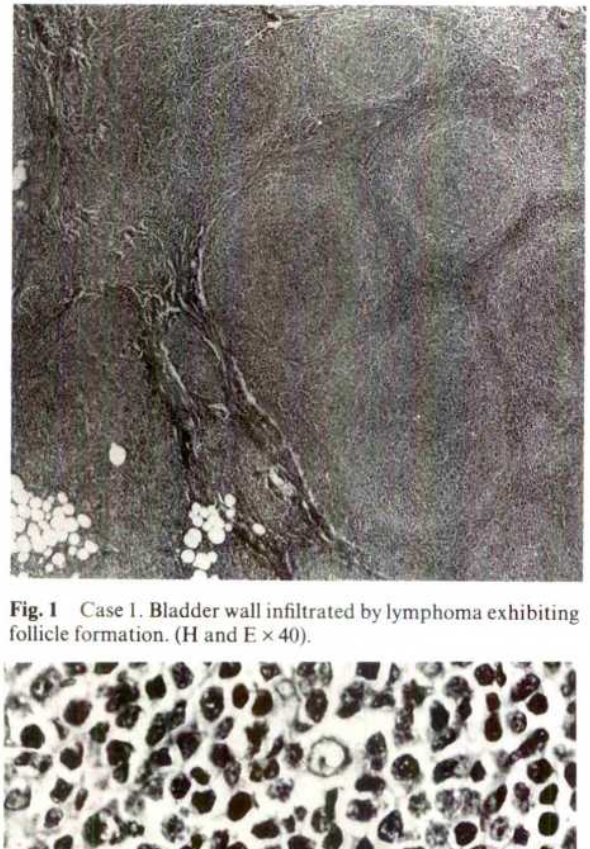

Fig. 1 Case 1. Bladder wall infiltrated by lymphoma exhibiting follicle formation. (H and E × 40).

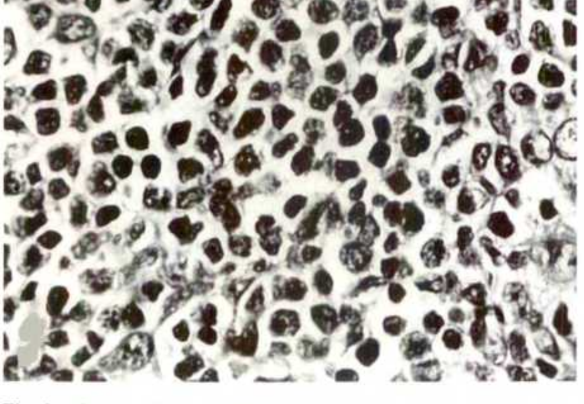

Fig. 2 Case 1. The predominant tumour cells are centrocytes. (H and E × 400).

Case 2. A 67-year-old white female presented with a 9-day history of haematuria, including blood clots. There were no abnormal physical signs apart from pallor. Investigations revealed a haemoglobin of 3.2 g/dl (3 weeks earlier it had been 10.5 g/dl). After transfusion, cystoscopy revealed a sessile tumour "the size of a small egg" in the right wall of the bladder and a biopsy was reported as a poorly differentiated malignant tumour. Eight weeks later a partial cystectomy was carried out, the mass being excised with a 1-cm margin. After the neoplasm had been identified as a lymphoma the patient was reassessed, but there was no clinical evidence of tumour elsewhere and radiological investigations (including CT scan of the pelvis and abdomen) were negative. She remained free of disease for 3 years and then developed confusion, right loin pain and expressive dysphasia. A CT scan of the brain showed tumour deposits in both cerebral hemispheres, which were irradiated. Her general condition continued to deteriorate and she died 39 months after her first presentation.

Examination of the partial cystectomy specimen revealed a sessile tumour 4.5 × 3.5 × 3 cm. Microscopy showed a diffuse infiltrate of large cells with single nuclei of irregular outline generally lacking clearly identifiable nucleoli (Fig. 3). The cytoplasm was scanty but strongly pyroninophilic. Mitotic figures were numerous. A few of the tumour cells showed cytoplasmic positivity with MT1 and an occasional cell expressed HLA DR, but the neoplasm was negative for all other immunohistochemical markers. It was classified as malignant lymphoma, centroblastic (diffuse, large cell) and therefore of high grade. It could not be established definitely whether it was of B or T cell origin.

At autopsy, massive retroperitoneal tumour recurrence was found which extended along the abdominal aorta to the coeliac axis and destroyed the upper pole of each kidney. A 3-cm deposit was present in the spleen and there were multiple intracranial tumours up to 5 cm in diameter, involving the meninges and both cerebral hemispheres. There was no recurrence in the bladder.

Case 3. A 76-year-old white woman presented with vulval soreness, long-standing dysuria and an episode described as post-menopausal bleeding which caused her to seek medical advice. She did not complain of haematuria. She also suffered from arthritis and 12 years previously had received ^{131}I for hyperthyroidism.

On examination a large mass was found which surrounded the urethra and extended to the anterior vaginal wall. There was no enlargement of the liver, spleen or lymph nodes. Investigations revealed a haemoglobin of 6.9 g/dl and no other abnormality. At operation the mass was noted to be clear of bone and it was excised. She made a good recovery and received no further treatment. Two years after her initial presentation she

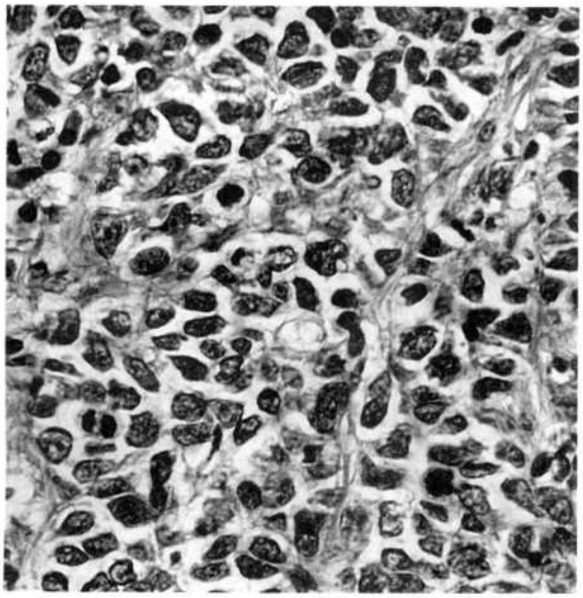

Fig. 3 Case 2. The predominant tumour cells are large lymphoid cells, similar to centroblasts. (H and E × 400).

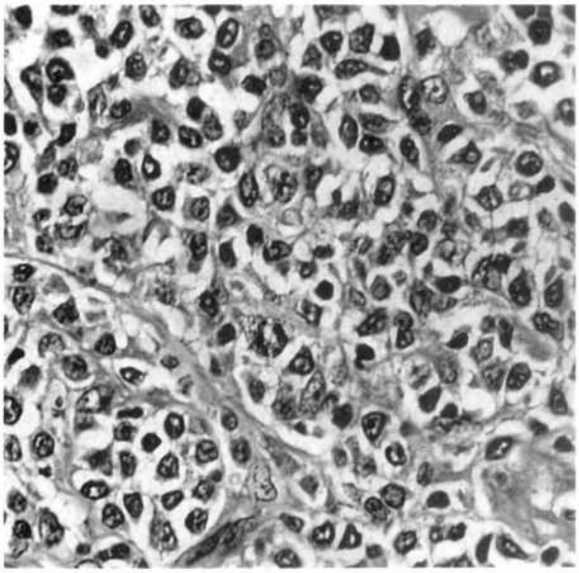

Fig. 4 Case 3. The tumour comprises both centrocytes and centroblasts. (H and E × 400).

remains well with no evidence of local recurrence or disseminated disease.

Examination of the excised specimen showed a 5.0 × 4.5 × 2.5 cm tumour surrounding the urethra. Microscopy revealed a diffuse infiltrate of neoplastic cells deep to the urothelium. It was composed of centrocytes (small cleaved follicle centre cells) with fairly numerous centroblasts (large follicle centre cells) and a small number of immunoblasts (Fig. 4). Rare mitotic figures were seen. There was no follicle formation. The tumour was classified as a malignant lymphoma, mixed centrocytic and centroblastic with a diffuse pattern (diffuse, mixed small and large follicle centre cell) and therefore of low grade. Immunohistochemistry showed a strong positive reaction for Common Leukocyte Antigen, L26 and MB1, which indicated a lymphoma of B cell origin.

Review of the Literature

In contrast to primary malignant lymphoma of the prostate and male urethra, which are uncommon but well recognised entities (Heaney *et al.*, 1985), we have found only 2 reports ascribing the origin to the female urethra. The first case was a reticulum cell sarcoma in a Japanese woman (Pak *et al.*, 1980). The second patient was a 63-year-old Algerian woman with dysuria, vulval pruritus and a 7-cm mass at the urethral orifice, which histology revealed to be a well differentiated lymphocytic lymphoma. The disease was localised and complete remission occurred after chemotherapy (Touhami *et al.*, 1987).

Primary malignant lymphomas of the bladder are rare and only 64 cases have been reported, plus our 2 cases which fulfil the criteria of localised disease at the time of diagnosis. Where stated, the sex ratio was 26 males (45%) to 32 females (55%) and the average age at diagnosis was 58.7 years (range 20–81). Cases have been reported from Europe, North and South America, Australasia and 1 from Japan (Gohji *et al.*, 1985) but none from Africa, the rest of Asia or the Middle East. Where race was stated, all patients (with the presumed exception of the Japanese case) were described as white or Caucasian.

Most clinical details have been recorded in 63 cases. The commonest presenting symptom was haematuria in 50 patients (79%). This was often severe, with passage of blood clots, and of short duration. Fourteen patients (22%) complained of separate or associated dysuria and 11 (17%) of frequency. Relatively rare presenting symptoms included abdominal pain, reduction in stream and systemic changes such as weight loss. In 3 patients, including 1 of our own, the diagnosis was made incidentally on a follow-up cystoscopy. A long history of cystitis was documented in 14 patients (22%).

The operative or macroscopic appearance was usually of one or more solid, round, tumour-like masses, often with ulceration of the overlying mucosa. Histological descriptions reflect the nomenclature fashionable at the time. Three were called plasmacytoma (Marion and Leroux, 1924; Auvigne *et al.*, 1956; Chaitin *et al.*, 1984) and a further 2 were labelled Hodgkin's disease (Lebowich, 1937; Marconis, 1959). Most of the rest were described as lymphosarcoma (and more recently lymphoma), usually mentioning a combination of small and large lymphoid cells. Follicle formation was recorded in 14 of the 59 cases (25%) with a histological description. Immunohistochemistry was done on 6 cases but was largely restricted to the demonstration of immunoglobulin light and heavy chains (Forrest *et al.*, 1983; Chaitin *et al.*, 1984; Heaney *et al.*, 1985; Gohji *et al.*, 1985; de Bruyne *et al.*, 1987).

Some details of treatment were available in 54 patients. The tumour was resected (either by a partial cystectomy or transurethrally) in 33 (61%) and total cystectomy was performed on 8 (15%). Some form of radiotherapy was given shortly after diagnosis in 32 cases (59%). Six patients received chemotherapy.

The prognosis was generally good. Thirty-nine of 54 patients (72%) were alive and free of disease at the time of being reported; the average follow-up was 46 months and 1 patient was alive and well after 13 years (Parton, 1962). Another patient died of a cerebral haemorrhage 5 years after diagnosis with no evidence of lymphoma (Wagner, 1941). Eleven of 54 patients (20%) died of the disease (range 2–55 months, mean 13) and 2 were alive with recurrent tumour 74 months (Elizade *et al.*, 1965) and 36 months (Aigen and Phillips, 1986) after diagnosis. Another patient died of a pulmonary embolism 19 days after being diagnosed. Post mortem examination showed lymphoma restricted to the bladder (Gupta *et al.*, 1985).

Correlating survival with histological descriptions is fraught with too many variables to be of general value. Nevertheless, all patients with follicular lymphoma were still alive at the time of publication (range 6–84 months). The one definitely high grade neoplasm was an immunoblastic lymphoma (Forrest *et al.*, 1983). The patient was still alive but had been followed up for only 3 months.

In considering the effect of treatment a large number of variables enter the equation, not least the different techniques available now compared with 30 or more years ago. The extent of surgery seems irrelevant, since similar proportions died or had recurrences regardless of whether total cystectomy (25%), partial cystectomy/resection (15%) or neither (23%) had been performed. Of the 32 patients given radiotherapy soon after diagnosis, only 3 were noted to have died of disease (Maloney, 1947; Marshall and Dooley, 1952; Lewi, 1986) compared with 8 of the 22 where radiation was given either late or not at all. Chemotherapy was given to only 6 patients (Winter *et al.*, 1979; Chaitin *et al.*, 1984; Gohji *et al.*, 1985; Heaney *et al.*, 1985; Lewi *et al.*, 1986; De Bruyne *et al.*, 1987).

Discussion

A few extranodal non-Hodgkin's lymphomas belong to well defined clinicopathological entities such as Burkitt's tumour or *Mycosis fungoides*. A significant proportion of the remainder have been described as arising in mucosa-associated lymphoid tissue (MALT) (Isaacson and Spencer, 1987). These include neoplasms originating in indigenous lymphoid tissues, as in the intestine or lung, and those arising in chronic inflammatory conditions, often of an autoimmune nature. Examples of the latter are thyroid lymphomas in Hashimoto's disease and salivary gland neoplasms in Sjogren's syndrome. To these can possibly be added uterine lymphomas which, although rare, usually occur in the cervix (Harris and Scully, 1984), commonly the site of chronic inflammation although not autoimmune. Should lower urinary tract lymphomas be included amongst the MALTomas? Since there is no substantial naturally occurring lymphoid tissue at this site, such a hypothesis must be based on pre-existing chronic inflammation as a source. However, only 22% of patients had a history of chronic cystitis and, in most cases, convincing histological evidence of long-standing inflammation was lacking. It is also noteworthy that no case of primary lymphoma has been recorded in a neurogenic bladder. Therefore, whilst a few urinary tract lymphomas could conceivably be considered as MALTomas, most should not.

The next question that arises is whether urinary tract lymphomas are underdiagnosed. On a large scale, this is unlikely. Most lymphomas should be broadly identified as such by the majority of surgical pathologists on haematoxylin and eosin stained sections alone, provided adequate tissue is available for study. However, some uncommon neoplasms, *e.g.* small cell carcinomas, may mimic lymphoma (Mills *et al.*, 1987). In such cases, immunohistochemical markers help to identify the epithelial or other nature of the tumour (van Eyken *et al.*, 1987).

Immunohistochemistry is also necessary to identify the cell of origin. Reagents for B and T cells that are reasonably effective on paraffin sections are now available (Hall *et al.*, 1988). In the present study, 2 patients had B cell lymphomas. The 6 other patients in whom immunohistochemistry was carried out all expressed surface immunoglobulins. Amongst the rest, follicle formation also indicated a B cell origin, but there is insufficient evidence in the remainder to suggest whether they were T or B cell neoplasms.

In conclusion, primary lymphoma of the lower urinary tract is a truly rare neoplasm, although modern techniques may identify slightly more cases than was previously possible. In assessing prognosis, the histological grade is probably of value, particularly follicle formation. With regard to treatment, radiotherapy appears to be of value, but there is as yet insufficient information of chemotherapy.

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Does Urethral Instrumentation Affect Uroflowmetry Measurements?

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Summary—Uroflowmetry was performed before and after urethral catheterisation in 129 patients. Uroflowmetry measurements were significantly modified by urethral instrumentation. In males, both maximum and mean flow rates decreased following urethral catheterisation, while in females only the maximum flow rate decreased, the mean flow rate remaining unchanged. Voided volume increased (and consequently resdidual urine decreased) in females after catheterisation, but did not change significantly in males. False positive results were encountered in 32% of patients and false negative results in 11% when flowmetry was done immediately after catheterisation. Uroflowmetry after urethral instrumentation is not recommended.

Uroflowmetry is widely used as a screening test to evaluate lower urinary tract function. To be reliable, it has been recommended that the minimum voided volume should be at least 100 ml (Ryall and Marshall, 1982; Marshall *et al.*, 1983). It is not unusual, however, to encounter patients who are unable to void this amount. In a series of 55 males aged 60 years or more, 41% had never passed more than 150 ml per void and half of these had never exceeded 100 ml (George *et al.*, 1981).

It is tempting, in these cases, to fill the patient's bladder to capacity via a urethral catheter and then let the patient void spontaneously in a flowmeter. However, before considering the validity of a flow curve so obtained, it is necessary to ascertain that urethral catheterisation does not have a significant influence on uroflow measurements. Reports on this subject are few and their conclusions contradictory (Nordling *et al.*, 1981; Lief *et al.*, 1984) so we decided to conduct our own study, including patients of both sexes.

Patients and Methods

In this prospective study we analysed the uroflow data of 129 patients (82 males and 47 females) with a mean age of 53 years (range 15–79). Patients with various clinical symptomatology, where uroflowmetry as a screening or diagnostic procedure was felt to be useful, participated in the study. Those who were unable to void at least 100 ml spontaneously at the first flowmetry were excluded.

Patients were instructed to present at the uroflowmeter with a normal desire to void. After this spontaneous voiding, a well lubricated 16 F Nelaton rubber catheter was passed into the bladder via the urethra and the post-voiding residual urine was measured. Then, using this same catheter, the bladder was filled by gravity with a normal saline solution at room temperature to a volume equal to the sum of the voided volume and the residual urine. The catheter was then withdrawn and the patient asked to void spontaneously in the flowmeter. The residual urine after the second flowmetry was calculated by subtracting the voided volume from the total volume instilled into the bladder.

For each voiding event the voided volume, maximum flow rate, mean flow rate and residual urine were measured. For each individual curve the maximum flow and mean flow were reported on a nomogram (Siroky *et al.*, 1979, 1980) in order to determine the presence or absence of obstruction.

Since all data (except for residual urine) followed a normal or nearly normal distribution, the paired and unpaired Student's *t* test was used for statistical analysis.

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Results

In the group considered as a whole, there was a significant decrease ($P=0.000$) in the maximum and mean flow rates after urethral catheterisation (Table 1). There was also a significant rise in the voided volume following instrumentation. Almost the same results were found in the male group (Table 2) except for voided volume, which did not change significantly. In the female group (Table 3), there was a significant increase ($P=0.004$) in the voided volume and a significant decrease ($P=0.002$) in the maximum flow rate after instrumentation. The mean flow rate remained unchanged.

A false positive result was defined as an obstructed curve on the second uroflowmetry, when the first curve showed no obstruction, and a false negative result was defined as a non-obstructed curve on the second uroflowmetry, when the first curve showed obstruction. Thus the false positive rate for the total patient population was 28% (21/76 patients obstructed) and the false negative rate was 13% (7/53 patients obstructed after instrumentation). Separate rates for the male and female groups are shown in Table 4.

Table 1 Uroflow Measurements Before (a) and After (b) Urethral Instrumentation

Measurements	*No. of patients*	*Mean (±1 SD)*	*P*
Volume (ml)	129	(a) 294 (155) (b) 314 (163)	0.016
Max. flow rate (ml/s)	129	(a) 20 (10) (b) 16 (8)	0.000
Mean flow rate (ml/s)	129	(a) 10 (5) (b) 8 (5)	0.000

Table 2 Uroflow Measurements Before (a) and After (b) Urethral Instrumentation in Male Patients

Measurements	*No. of patients*	*Mean (±1 SD)*	*P*
Volume (ml)	82	(a) 295 (165) (b) 305 (171)	0.316
Max. flow rate (ml/s)	82	(a) 18 (10) (b) 14 (7)	0.000
Mean flow rate (ml/s)	82	(a) 9.4 (5.0) (b) 7.6 (4.0)	0.000

Table 3 Uroflow Measurements Before (a) and After (b) Urethral Instrumentation in Female Patients

Measurements	*No. of patients*	*Mean (±1 SD)*	*P*
Volume (ml)	47	(a) 293 (139) (b) 328 (148)	0.004
Max. flow rate (ml/s)	47	(a) 23 (10) (b) 20 (9)	0.012
Mean flow rate (ml/s)	47	(a) 11 (5) (b) 10 (4)	0.057

Discussion

The influence of urethral catheterisation on uroflow measurements has not been extensively studied in the literature and we found only 2 such studies.

Nordling *et al.* (1981) presented 30 male patients who underwent uroflowmetry before and after urethral catheterisation using a 16 F Foley catheter; the bladder volume was found to be identical in the same patient during both procedures. They stated that both maximum and mean flow rates could vary considerably from spontaneous voiding to voiding after urethral instrumentation, but they were unable to demonstrate any specific trend in this variation. However, the data were not submitted to statistical analysis. Despite this observation, they concluded that urethral catheterisation using a 16 F catheter did not affect urinary flow measurement in male patients.

Lief *et al.* (1984) submitted 28 patients to uroflowmetry before and after cystometry. In about one-third of their patients (9/28) they noted a significant change in maximum and mean flow rates. It should be noted, however, that none of these patients had

Table 4 False Positive and False Negative Rates in the Male (A) and Female (B) Populations

	After instrumentation		
	Obstructed	*Non-obstructed*	*Total*
(A) Males			
Obstructed	38	5	43
Non-obstructed	14	25	39
Total	52	30	82
(B) Females			
Obstructed	17	2	19
Non-obstructed	7	21	28
Total	24	23	47

Males: False positive: 14/52 (27%)
False negative: 5/30 (17%)
Females: False positive: 7/24 (29%)
False negative: 2/23 (9%)

the same bladder volume prior to micturition, making comparison difficult. It is recognised that maximum flow and mean flow increase with increasing voided volume. Our study demonstrated a significant decrease in maximum and mean flow rates following urethral catheterisation when the patient population was considered as a whole. The observation that voided volume increased significantly during the second micturition adds even more significance to the decrease in flow. The fact that voided volume increases after urethral manipulation also implies that post-voiding residual urine decreases. This is important to remember, because therapeutic decisions can be influenced by the presence or absence of significant post-voiding residual urine (George, 1986).

Maximum flow rates are considered to be less reliable than mean flow rates on successive flowmetry curves in the assessment of voiding dysfunction. From one voiding to the other, the maximum flow rate can be increased by abdominal straining. This same abdominal straining, however, will affect to a lesser degree the mean flow rate. Furthermore, flow rates can be more readily increased than decreased voluntarily. Thus a decrease in maximum and mean flow rates can be considered even more significant.

This study has indicated that uroflow measurements are modified in a different way in males and females after urethral manipulation. The maximum flow rate is significantly altered in both groups, but mean flow rates decrease more significantly in the males ($P = 0.000$) than in the females, where the difference is not statistically significant ($P = 0.057$). This difference could be secondary to urethral oedema over a longer distance in males, so creating a greater resistance to flow, according to Poiseuille's law.

Clinicians currently use nomograms to assess the obstructive nature of a given flow curve. If our patient population is divided into obstructed and non-obstructed groups, based on such a flow nomogram (Siroky *et al.*, 1979), it appears that among those who were obstructed before instrumentation 11% showed a non-obstructed flow curve (false negatives) after instrumentation. Among the initially non-obstructed patients, 32% became obstructed (false positives) following urethral instrumentation (Table 4). Table 5 shows the data when males and females are considered separately. It should be noted that false positives outnumbered false negatives (Table 4). This means that urethral catheterisation induced an obstructive curve more often in patients with previously normal uroflowmetry and catheterisation produced a normal flow curve less often in an obstructed patient. No statistically significant factors have been found to predict which individual patient will see his (or her) flowmetry curve modified by urethral manipulation.

In conclusion, urethral instrumentation has a significant but unpredictable effect on uroflowmetry measurements. It is inadvisable to perform uroflowmetry immediately after urethral instrumentation.

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Prostate Tumour Markers as an Aid in the Staging of Prostatic Cancer

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Summary—Serum acid phosphatase activity (ACP), prostate specific phosphatase (PAP) and prostate specific antigen (PSA) were measured in 100 patients with prostatic cancer. The patients were divided into 4 groups: T1–2 MO, T3–4 MO and M1 patients with ≤ 10 or > 10 metastatic foci in bone scintigraphy. The mean serum ACP levels were almost identical in the T1–2 MO and T3–4 MO groups and there was no significant difference between the mean PAP values. Significantly higher PSA levels were observed in the MO patients in the extracapsular category compared with those in the intracapsular category. The mean serum levels of all 3 tumour markers were significantly higher in the M1 than in the MO category. PSA seems to be the marker of choice as a diagnostic aid for differentiating between patients with intracapsular and those with extracapsular tumour growth. In prostatic cancer patients with bone metastases these markers were of similar value for staging the disease.

Tumour markers for prostatic cancer are known to be elevated in most patients with metastatic disease (Gutman and Gutman, 1938; Ahmann *et al.*, 1987; Romas, 1987). Recent analytical improvements have raised the hope that these markers could be applied to the early detection of prostatic cancer and to accurate staging of the disease (Chu and Murphy, 1986; Romas, 1987). Theoretically, the volume of the primary tumour and/or its metastases should correlate with the serum levels of the tumour markers. We have investigated the usefulness of serum acid phosphatase activity, specific prostatic acid phosphatase and prostatic specific antigen in the staging of prostatic cancer.

Patients and Methods

The study comprised 100 patients, aged 53 to 91 years (mean 70), with histologically verified prostatic cancer. The stage of the tumour was determined according to the UICC (1987) classification. The MO category was subdivided into an intracapsular (T1–2) and an extracapsular (T3–4) group. Transrectal ultrasound was carried out in all patients to define more accurately the local stage. The patients also underwent scintigraphy. Total prostatectomy was performed in 16 cases and 8 of these patients underwent computed tomography (CT) pre-operatively. The final staging of the 16 patients undergoing surgery was based on postoperative histopathological examination of the prostate. Bone metastases were identified by scintigraphy, using a large field-of-view gamma camera equipped with whole body imaging devices. Each patient was imaged 3 h after an intravenous dose of approximately 600 MBq of ^{99m}Tc-labelled dicarboxypropane diphosphate (Hoechst, FRG). The scans were evaluated by 2 physicians without knowledge of the serum levels of the tumour markers. The M1 patients were divided into 2 categories according to the degree of bone involvement (≤ 10 or > 10 foci) as determined by scintigraphy (Liewendahl *et al.*, 1984). The classification into M1 cases was not based solely on the level of serum tumour markers.

Serum samples for the assay of tumour markers

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were collected before treatment and stored at −20°C until assayed. All assays were performed in duplicate.

Serum acid phosphatase activity was measured using *p*-nitrophenyl phosphate as substrate (Bessey *et al.*, 1946). The upper limit of the reference range, defined as the mean +2 SD, was 13 iu/l.

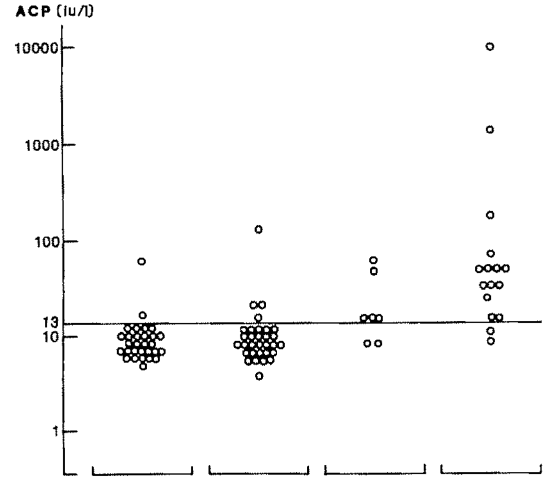
For radioimmunoassay of serum prostatic acid phosphatase, the method of Vihko *et al.* (1980, 1981) was used. The upper limit of the reference range, defined as mean +2 SD, was 3.2 µg/l.

Serum prostate specific antigen was determined by an immunoradiometric assay, using 2 cut-off limits of 2.7 and 10 µg/l. Reagents were obtained from Hybritech Inc. (San Diego, USA).

The significance of differences in the mean levels of the various tumour markers, after logarithmic transformation of the results, was assessed by Student's *t* test. The analysis of variance was applied whenever appropriate. The diagnostic accuracy of the different assays was evaluated with the test of McNemar.

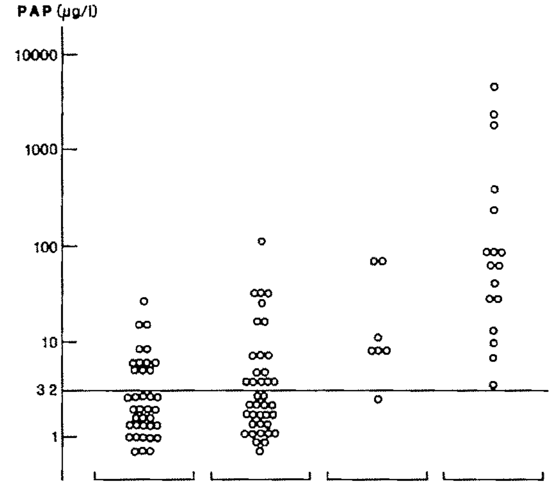
Results

The distribution and the corresponding upper reference limits of serum ACP, PAP and PSA levels in the various clinical categories are presented in Figures 1, 2 and 3. There was a highly significant correlation ($P<0.001$) between tumour volume and serum levels of all 3 markers. The mean serum levels of ACP, PAP and PSA were significantly higher ($P<0.001$) in the M1 than in the MO category.



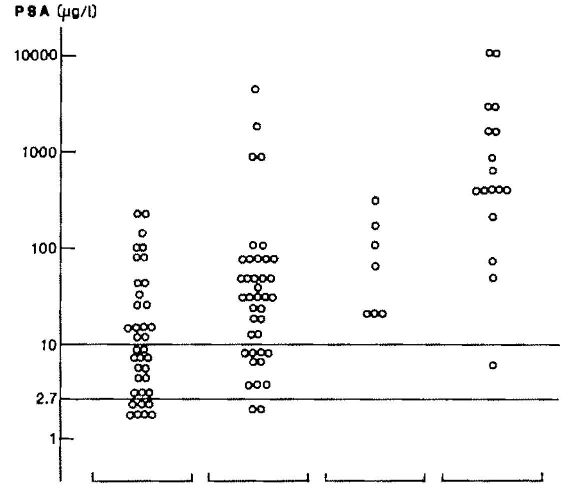
Clinical stage	T1–2MO	T3–4MO	M1 (1-10 mts)	M1 (>10 mts)
No. of patients	29	31	7	16
Mean	8.7	9.6	19.4	65.5
+2 SEM	10.3	11.9	34.9	160.9
−2 SEM	7.3	7.8	10.8	26.7

Fig. 1 Distribution of serum ACP levels in patients with carcinoma of the prostate in relation to clinical stage. Cut-off limit 13 iu/l.



Clinical stage	T1–2MO	T3–4MO	M1(1-10 mts)	M1(>10 mts)
No. of patients	37	39	7	17
Mean	2.5	3.6	12.8	84.9
+2 SEM	3.3	5.1	32.4	231.6
−2 SEM	1.8	2.4	5.0	31.1

Fig. 2 Distribution of serum PAP levels in patients with carcinoma of the prostate in relation to clinical stage. Cut-off limit 3.2 µg/l.



Clinical stage	T1–2MO	T3–4MO	M1 (1-10mts)	M1 (>10 mts)
No. of patients	37	39	7	17
Mean	11.6	32 6	63.8	566 8
+2 SEM	18.5	56.9	150.6	1425.9
−2SEM	7 3	18.8	26.9	226.3

Fig. 3 Distribution of serum PSA levels in patients with carcinoma of the prostate in relation to clinical stage. Cut-off limits 2.7 and 10 µg/l.

Among the M1 patients, those with more than 10 bone foci had higher serum levels of all 3 markers

($P < 0.01$) than those with less than 10 foci. There were no significant differences ($P > 0.05$) in the mean ACP, PAP and PSA levels between patients in the T3–4 MO group and those in the M1 group (≤ 10 foci).

The mean serum levels of ACP were almost identical in the T1–2 MO and T3–4 MO categories. There was no significant difference in the mean PAP values between the intra- and extra-capsular categories ($P > 0.05$). Patients in the T3–4 MO group had a significantly higher mean PSA level ($P < 0.05$) than those in the T1–2 MO group.

The sensitivity and specificity in differentiation between the T1–2 MO and T3–4 MO categories were 13 and 93% for ACP and 44 and 68% for PAP respectively. With the upper cut-off limit of 2.7 μg/l, the respective figures for PSA were 95 and 19%. If the upper cut-off limit was set at 10 μg/l, the sensitivity and specificity of PSA were 72 and 51%. The corresponding accuracy figures were 10, 38, 88 and 61%.

Discussion

Determination of acid phosphatase enzymatic activity has been the standard laboratory method for the detection of prostatic cancer for many years. The sensitivity of this method, after analytical improvements, is now generally 70 to 80% in metastatic (stage D) disease (Guinan *et al.*, 1987). However, its sensitivity is much lower in intracapsular patients and in those with local extraprostatic growth. Radioimmunoassays and enzyme immunoassays for prostatic acid phosphatase are known to be more specific and sensitive than the traditional enzymatic methods (Oosterom *et al.*, 1986). It was therefore expected that immunoassays might be useful not only in detecting metastases but also in demonstrating non-metastatic primary tumours. Most investigators, however, agree that serum PAP concentration is usually within normal limits in intracapsular prostatic cancer (Romas, 1987). Therefore, if the prostate specific antigen level is already above normal in intracapsular prostatic cancer, this test would serve as an important additional tool in the staging of prostatic cancer. It is essential to identify the T1–2 NO MO patients, since radical (and therefore curative) surgery is possible only in these cases.

In the present study, patients were divided into 4 groups according to the local growth of the primary tumour and the degree of bone involvement. There was a clear correlation between serum ACP, PAP and PSA levels and stage of the disease.

The M1 group included patients with a small (≤ 10) or large (≥ 10) number of bone metastases. The mean levels of ACP, PAP and PSA for the former category were significantly lower than for the latter. PAP and PSA were only slightly better than ACP for the purpose of staging untreated prostatic cancer patients with advanced disease. When a prostatic cancer patient has been diagnosed by scintigraphy as having bone metastases, no essential additional information can be obtained by determination of serum tumour markers, except in patients with equivocal scintigraphic findings.

The diagnostic sensitivity of PSA for low stage disease has been well documented (Oesterling *et al.*, 1987). In the present study, the mean PSA value was significantly higher in the T3–4 MO than in the T1–2 MO category. The same trend was observed for the mean PAP values, although the difference was not statistically significant. Samuel *et al.* (1984) showed that ACP levels are seldom elevated in intracapsular tumours. Our results confirm this finding, for only 10% of patients in the intracapsular category had elevated ACP levels. A correlation between capsule penetration and elevation of serum PAP levels was reported by Salo and Rannikko (1988). In this series, 38% of the MO patients had elevated PAP levels, but the difference in mean serum values between the intra- and the extra-capsular categories was not significant.

Our results show that PSA is a more sensitive marker of low stage disease than the other 2 markers. The lower cut-off level (2.7 μg/l) ensures that sensitivity is much higher, but it remains high even when the cut-off limit is raised to 10 μg/l. For clinical purposes a cut-off level exceeding 2.7 μg/l is indicated because a significant number of patients with benign prostatic hyperplasia have serum concentrations above this level; Stamey *et al.* (1987) proposed a compromise level of 4 μg/l. In the present series the sensitivity of differentiation between the T1–2 MO and T3–4 MO categories fell from 95 to 72% when the cut-off level was raised to 10 μg/l and the specificity of PSA (51%) was even lower than that of ACP (93%) and PAP (68%). This is further confirmation that, for clinical purposes, the most appropriate level for PSA is between these 2 extremes (2.7–10 μg/l).

When comparing the accuracy figures, PSA with a reference limit of 2.7 μg/l (88%) was more reliable than ACP (10%), PAP (38%) and PSA with a reference limit of 10 μg/l (61%). By combining the high sensitivity of PSA and the high specificity of ACP, we can most reliably identify the intracapsular tumours and thus identify those patients suitable for radical surgery. It is probable that patients with normal PSA levels (<2.7 μg/l) have an intracapsular tumour. It is likely that patients with elevated PSA but normal ACP levels also have organ-confined prostatic cancer.

We have concluded that serum levels of ACP, PAP and PSA correlate with the stage of prostatic cancer. In prostatic cancer patients with bone metastases, none of these tumour markers is superior to any other as an aid in clinical staging; although ACP may be more cost-effective. However, a more important goal in clinical practice is the reliable identification of T1–2 MO prostatic cancer patients, since curative surgery is possible only when the primary tumour is intracapsular. In this respect PSA appears to be the marker of choice because it is the most sensitive for low stage disease. Before definite conclusions on the usefulness of PSA can be drawn, more studies aimed at defining the appropriate cut-off limit are required. The effect of age and benign prostatic hyperplasia must be considered when the most clinically useful limits for PSA are determined.

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Erythrocyte Stearic to Oleic Acid Ratio in Prostatic Carcinoma

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Summary—The red cell membrane stearic acid to oleic acid ratio was analysed in 34 men with histologically proven carcinoma of the prostate and distant metastases. This ratio was expressed as the saturation index (SI). A mean SI of 0.97 was found in control patients without evidence of any malignancy whereas all patients with advanced prostatic cancer showed a reduced stearic to oleic acid ratio (mean SI 0.466). Untreated patients had a significantly lower SI (mean 0.36) than those who had responded to hormonal therapy (mean 0.547; $P<0.0001$). A drop in SI correlated well with more advanced disease as judged by radiological findings and serum PSA.

It is suggested that red cell membrane SI correlates well with radiological and biochemical markers of advanced prostatic carcinoma and may be used as a marker to assess progress and response to treatment.

Carcinoma of the prostate is now the second commonest cause of death from cancer in men in the United Kingdom. A total of 7500 new cases are diagnosed annually and the incidence of the disease appears to be increasing. Since 60% of patients present with established metastases, the prognosis is poor. The most efficacious treatment is androgen withdrawal either by orchiectomy, oestrogens, LH-RH analogues or antiandrogens. Response rates of up to 80% can be expected after treatment and on average the response will last for 12 months before relapse occurs. It would be valuable to have an indicator of response and prognosis for patients with advanced prostatic cancer.

It is now well established that the properties of plasma membranes of transformed and malignant cells differ from those of normal cells (Wood *et al.*, 1985a; Habib *et al.*, 1987). A general and concurrent finding has been that in the malignant cell there is an increased membrane fluidity (as judged by fluorescent probe and magnetic resonance analysis). These changes have been found to occur not only in the cell membranes of the malignant tissue itself but also in the cell membranes of erythrocytes from patients with malignancy. The increased membrane fluidity is due to a higher content of unsaturated fatty acids than in normal cells. It has also been shown that the major change in the fatty acids is in the stearic and oleic acid fractions and that the ratio of these 2 fatty acids could be used as an index of fatty acid saturation in the cell membrane (referred to as the "saturation index" (SI)).

We present the results of a study of the cell membrane fluidity of red cells in patients with advanced prostatic cancer and the significance of the primary findings is discussed.

Patients and Methods

A total of 34 men with histologically proven carcinoma of the prostate were studied; 30 had metastases, 2 had liver metastases and 2 had locally advanced tumours with pelvic lymph node involvement. In 11 cases no treatment had been given. Seventeen patients were undergoing hormone treatment, 9 with the antiandrogen cyproterone acetate and 8 with a combination of cyproterone acetate and an LH-RH analogue. Six other patients had progressive disease following previous hormonal therapy. Five cases were studied sequentially before

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and after treatment. Twelve healthy male volunteers were taken as controls.

A 5 ml blood sample in EDTA was taken from all patients and centrifuged at 1000 rpm to precipitate red blood cells. All samples were stored at −20°C until processed. Total lipid extraction was carried out following the method used by Apostolov and Barker (1981) and Folch *et al.* (1957). The extracts were analysed by temperature programmed (160–260°C at 4/min) gas liquid chromatography of the fatty acid methyl-esters using a 2.1 × 2 mm 1D glass column packed with a 3% SP–2310/2% SP–2300 on 100/120 mesh chromosorb W (Supelco Inc). This allowed separation of C16, C18, C20 and C22 fatty acids. The stearic to oleic acid ratio was taken as the indication of membrane fluidity or saturation index.

Statistical analysis was performed using the Mann-Whitney U test.

Results

Normal male controls had a mean saturation index of 0.944 (range 0.86–1.057). In all 3 groups of patients, significantly lower ratios of stearic to oleic acid were found than in the control group ($P = < 0.05$). The untreated group exhibited significantly lower saturation indices (mean 0.485, range 0.34–0.59) than the group undergoing hormone treatment (mean 0.64, range 0.41–0.69) ($P = < 0.05$). There was no significant difference between the treated and the relapsed group (Fig. 1).

In all 5 patients in whom sequential pre- and post-treatment erythrocyte saturation indices were measured, a rise was seen after treatment commenced (Fig. 2). It was not possible with such small numbers to relate the saturation index to the grade or local stage of the tumour.

Further studies are required to look at the changes in prostatic tissue cell membrane fluidity in addition to red cell membrane fluidity.

Discussion

The cell membrane is an essential component of cellular homeostasis (Cooper, 1977), providing a fluid barrier to the passage of some components whilst facilitating transport of others. In general, higher membrane fluidity leads to increased cell metabolism and higher division rates (increased metabolism and capacity for division are the essential characteristics of malignant cells). The lipid bilayer determines the fluidity of the cell membranes. The degree of this fluidity is dependent

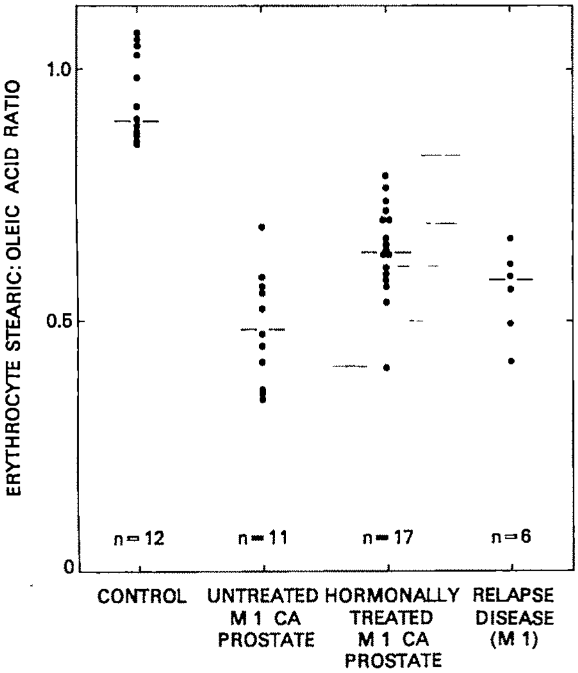

Fig. 1 Erythrocyte stearic:oleic acid ratio in controls and patients with advanced prostatic cancer.

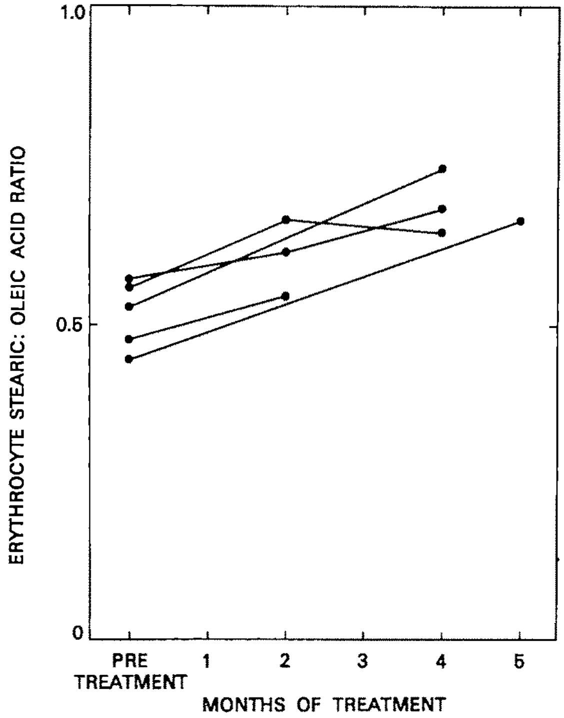

Fig. 2 Change in erythrocyte stearic:oleic acid ratio following hormonal therapy for advanced prostatic cancer.

on the ratio of saturated to unsaturated fatty acids: the greater the degree of unsaturation the more fluid the cell membrane. It has been shown that a significant decrease in cell membrane saturation occurs in liver tumour cells (Wood *et al.*, 1985a) and in leukaemic white blood cells (Apostolov *et al.*, 1985) as compared with normal cells. A similar change has been found in the circulating erythrocytes of patients with solid tumours (Wood *et al.*, 1985b), possibly due to an effect on the bone marrow produced by factors released by the tumour tissue. The available evidence suggests that a decrease in fatty acid saturation index is a feature of malignant transformation in human cells.

This study has confirmed that a decrease in fatty acid saturation is seen in patients with advanced prostatic carcinoma. Further study will be necessary to ascertain any relationship between tumour stage and grade and the level of desaturation. The study has also shown an increase in saturation index in patients after starting hormone treatment. This seems to imply a general beneficial effect of hormone treatment in patients with prostatic cancer. The reasons for these changes in erythrocyte fatty acid saturation have yet to be determined, but it seems to offer an opportunity for study of the mechanisms involved in prostatic carcinogenesis.

Membrane fluidity may play an important part in determining the spatial orientation of receptor molecules in the cell membrane. It would also be of interest to establish whether alterations in the fatty acid composition of the malignant cell membrane could alter receptor configuration and in so doing enhance or reduce the cell's affinity for hormonal interaction.

Further studies are being conducted in this field.

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De-differentiation with Time in Prostate Cancer and the Influence of Treatment on the Course of the Disease

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Summary—There is little information on histological changes in prostate cancer during the course of the disease. We have studied 74 patients with carcinoma of the prostate who required 2 transurethral resections of the prostate (mean interval between resections 2.4 years). They constituted 18.4% of all patients with carcinoma of the prostate presenting to our clinic between January 1978 and April 1988. All tumours were staged by conventional methods and graded using the Gleason system. The Gleason sum score in those patients with tumour in both specimens increased in 49, remained constant in 12 and decreased in 7.

Within this group were 34 patients who were treated expectantly. The mean Gleason sum scores in this group increased, with a concomitant increase in local tumour stage and development of metastases. Although this was not a randomised trial, there was no significant difference in survival between patients having "deferred" management and those treated immediately, either from time of diagnosis or from time of second resection. There was, however, a significant difference in the time to second resection, with the "deferred" group requiring repeat resection on average 1 year earlier.

This study confirmed the concept of tumour de-differentiation with time and showed that this phenomenon occurs in both treated and untreated tumours. Although overall survival was not influenced by the type of initial therapy or its timing, local progression, as assessed by the need for further TURP, occurred earlier in those not receiving immediate therapy.

The need for and the timing of therapeutic intervention in carcinoma of the prostate continues to cause debate. An understanding of the natural history of the tumour would help to make treatment decisions more logical.

The natural history of cellular differentiation in carcinoma of the prostate is not known. In particular, it is not known whether carcinoma of the prostate displays a spectrum of grades at inception or whether high grade tumours develop from previously well differentiated cancers as a histological expression of tumour progression (McNeal *et al.*, 1986). It is clearly not possible to know the grade of tumour at inception, but the grade at presentation may explain the various patterns of clinical progression as suggested by Whitmore (1984). Invasive tumours at presentation could either be due to de-differentiation in a low grade tumour or may represent a rapidly growing high grade lesion present from inception.

The aim of this study was to take a group of patients from whom 2 sets of comparable histological material had been obtained and to examine the changes in local tumour stage, metastatic status and histological grade. We were particularly interested in such changes in patients who had received no immediate treatment after diagnosis and we compared these findings with those in patients who had received immediate therapy. Treatment was determined by individual clinicians and not selected by randomisation.

Patients and Methods

The records of all patients attending the Prostate Clinic at the Western General Hospital between

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January 1978 and April 1988 were reviewed. Of the 402 patients who were diagnosed as having carcinoma of the prostate, 74 (18.4%) were found to have had 2 transurethral resections with a mean interval of 2.4 years (range 2–79 months) between them. Second resections were performed for recurrent outflow tract obstruction or haematuria. All patients in whom the diagnosis of carcinoma of the prostate had been made by needle biopsy, or in whom subsequent pathology was detected in such a manner, were excluded from the study on the grounds that 2 sets of comparable histological material were not available.

Tumours were staged clinically by rectal examination at the time of surgery. All submitted resected tissue was examined histologically and the degree of differentiation scored using the Gleason system (Gleason, 1966). All patients had a technetium (^{99}Tc) bone scan and estimation of prostatic acid phosphatase at the time of histological diagnosis.

The patients were reviewed every 3 months in a prostate cancer clinic. Clinical examination, including rectal examination, estimation of serum electrolytes and acid phosphatase, was performed. Bone scans and chest X-rays were performed every 6 months until they became positive. Following histological confirmation of the diagnosis, treatment was expectant in 34 patients. Thirteen patients with clinically localised disease had local radical radiotherapy and 29 had immediate hormonal manipulation either as anti-androgen therapy or subcapsular orchiectomy.

Statistical methods included chi-squared test, paired *t* test and survival analysis using log rank analysis (Peto *et al.*, 1977).

Results

The mean age of the patients was 73 years (range 51–86) and the group was normally distributed about this mean.

When the Gleason sum scores at the second resection were compared with those of the first, it was found that they had increased in 49 patients, remained constant in 12 and decreased in 7. Six specimens were found to contain no tumour at the second resection. Of these, 5 had initially been treated with radiotherapy and the sixth was described as benign, having initially been a well differentiated tumour (Gleason 1 + 1). This patient subsequently died of metastatic carcinoma of the prostate.

In the 68 patients with tumour in both TUR specimens, the mean Gleason sum score increased from 5.7 ± 2.0 (mean + standard deviation) to 7.1 ± 1.7 ($P < 0.0005$, paired *t* test) (Table 1). Figure 1 illustrates the changes according to 3 groups of sum scores.

Table 1 Time-related Changes in Mean Gleason Sum Score in Patients Treated either Expectantly or Immediately

	Whole group	*Deferred*	*Treated*
Gleason sum score at first resection (Mean + SD)	7.1 ± 1.7		

During the interval between resections, the T category showed a sustained increase in 42 patients (57%) and 21 (27%) developed positive bone scans. Changes in T category and metastatic status for the whole group are shown in Table 2.

At the end of the follow-up period (30 April 1988), 59 patients had died; 19 (32%) from the effects of prostatic malignancy, 8 from unrelated causes and in 32 the cause of death was unknown (Table 3).

Within the study group were 34 patients who were treated expectantly. For this subpopulation the Gleason sum scores at the second resection had increased in 23, remained the same in 5 and decreased in 5. One patient had no apparent tumour at the second resection but proceeded to die of metastatic prostate cancer. In the 33 patients with tumour in both specimens, the mean Gleason sum score increased from 5.1 ± 2.2 to 6.4 ± 1.7 ($P < 0{\cdot}005$, paired *t* test) (Table 1).

The outcome in the deferred patients was then compared with the outcome in those who had

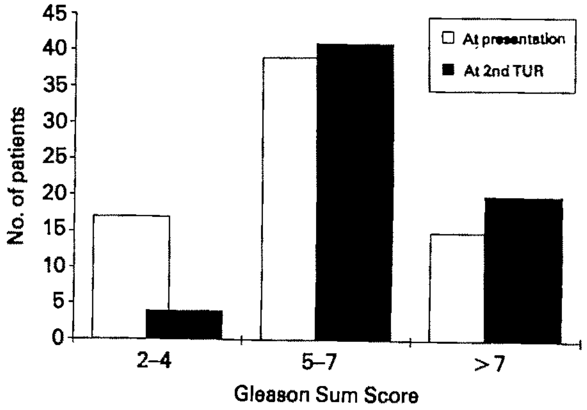

Fig. 1 Changes in Gleason sum score.

Table 2 T Category and Metastatic Status of Patients with Tumour at Time of First and Second Transurethral Resection

	Clinical stage (T category)					*Metastatic status*	
	T0	*T1*	*T2*	*T3*	*T4*	*M0*	*M1*
First TUR							
Whole group	13	3	20	30	8	42	30
Deferred	10	2	6	11	5	26	8
Treated	3	1	14	19	3	16	22
Second TUR							
Whole group	1	1	9	23	34	17	51
Deferred	0	1	5	8	19	14	19
Treated	1	0	4	15	15	3	32

Table 3 Cause of Death

	Deferred (N=34)	*Treated (N=40)*
No. dead	23	36
No. died from ca. prostate	8	11

Table 4 Survival Times

	Mean time to second resection (months)	*Mean time from second resection to death/date last seen (months)*
Deferred	21	24.5
Treated	33.5	19.7

received treatment immediately following diagnosis. Table 2 compares local tumour stage and metastatic status for the 2 groups both at presentation and at the time of second resection.

In both groups we examined the time to second TURP, the overall survival time from diagnosis and the survival from the time of second transurethral resection (Table 4). Although this was a retrospective, non-randomised study, the results indicate that the deferred group required further TUR sooner (on average 1 year sooner), survived longer following the second resection (often combined with hormonal therapy), but their overall survival was less than that of the treated group. Using probability curves, there is a significant difference between these groups in their time to second TURP ($P<0.001$) (Fig. 2). There was, however, no significant difference in survival between the treated and the deferred groups, either from time of diagnosis or from time of second resection.

Discussion

The results clearly show progression in T category, metastatic status and histological grade consistent with de-differentiation of the tumour with time. This is true both for those patients treated expectantly and those treated at the time of diagnosis. This observation confirms and extends the earlier work of Brawn (1983), who showed in a survery of 54 men, all treated with hormonal therapy and all having undergone 2 transurethral resections, that there was a 79% rate of de-differentiation of the tumour with time.

The association between tumour volume, tumour grade and metastatic potential was observed by Stamey *et al.* (1988). This observation has been confirmed in a combined necropsy and radical prostatectomy series of 138 patients where de-differentiation was strongly correlated with tumour volume (McNeal *et al.*, 1986). In the present series there was a sustained increase in T category in 42 patients (56.75%), 28 (67%) having an increase in the Gleason sum score but only 4 (9.5%) developing bony metastases. These results are similar to those reported by George (1988). In his series of 120 patients with M0 disease who were treated expectantly, local tumour progression was noted in 84% but only 11% developed bone metastases. However, within this same group were 23 patients who required a second transurethral resection (19%), only 1 of these patients developing bony metastases. This result is at variance with our findings, where 40% of our M0 patients had developed bony metastases by the time of second resection, and is probably explained by the short follow-up period

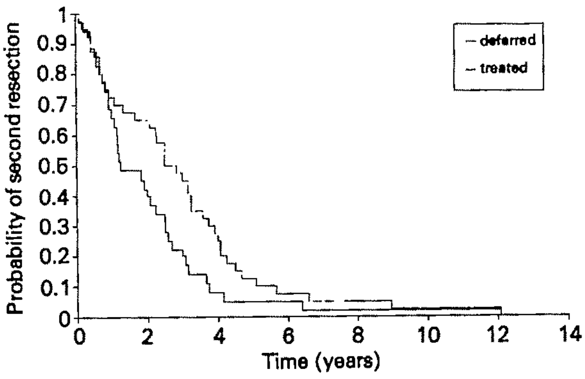

Fig. 2 Comparison of time to second TURP: deferred versus treated patients.

and the inclusion by George (1988) of a substantial proportion of patients with tumours which were incidental histological findings.

When the survival results between treated and deferred groups were reviewed, it appeared that the treated group had a longer overall survival. However, statistical analysis of the survival data showed no significant difference in survival either from time of diagnosis or from time of second resection. There was, however, a significant difference between the groups in the time to second resection. The groups were not selected for immediate or deferred therapy by random selection.

In conclusion, this study has shown that the natural history of carcinoma of the prostate, whether treated immediately or expectantly, is to de-differentiate with time. Furthermore, patients who either choose or are prescribed deferred treatment are likely to need a second TUR before those undergoing immediate treatment. It is not known whether this is due to lack of treatment or whether it reflects inherent differences in tumour behaviour.

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Megestrol Acetate in Relapsed Carcinoma of Prostate

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Summary—A series of 22 patients with advanced carcinoma of the prostate who had failed first-line hormonal therapy (orchiectomy, stilboestrol, luteinising hormone-releasing hormone agonist) were treated with 160 mg megestrol acetate daily. Treatment was well tolerated, side effects were minimal and 21 patients were evaluable. There were no complete or partial responses, although 8 patients had a good subjective response. In 6 patients the disease was stabilised for 6 to 12 months and there was a 40 to 50% reduction in their prostatic acid phosphatase (PAP) levels. It was concluded that megestrol acetate has a role as second-line hormonal therapy in the management of prostatic carcinoma.

One of the possible causes of relapse in prostatic carcinoma is the presence of circulating adrenal androgens which are not blocked by first-line hormonal therapy. Adrenal androgens are converted in prostatic cells to dihydrotestosterone (DHT), which is the major endogenous stimulus for prostatic carcinoma. Megestrol acetate is a synthetic progestogen with no oestrogenic or androgenic properties (David *et al.*, 1963) which both suppresses adrenal androgen production and blocks androgen receptors at the tumour cell level. In addition, it has an inhibiting effect on 5α reductase, responsible for the conversion of testosterone to DHT.

Geller (1985) summarised the role of megestrol acetate in prostatic carcinoma and various authors (Johnson *et al.*, 1975; Geller *et al.*, 1978; Bonomi *et al.*, 1985) reported response rates of 25 to 50% in previously untreated patients.

Patients and Methods

From January 1985, 22 patients with advanced prostatic carcinoma who had failed first-line hormonal treatment (as demonstrated by bone scan, X-rays or continuous rise of PAP over the previous 3 months) were included in the study. Details of their previous treatment are shown in Table 1. All had a life expectancy exceeding 3 months and a performance status of 0 to 3 on the ECOG scale (WHO Handbook, 1979) (Table 2). Patients were investigated by bone scan, skeletal X-rays, prostatic acid phosphatase levels, urea and electrolytes, liver function tests and full clinical examination.

A single daily oral dose of 160 mg megestrol acetate was given until the first sign of disease progression, radiologically or clinically, or until there was a 50% increase in PAP levels.

All patients were assessed monthly by full clinical examination and biochemical estimations, including PAP levels; bone scans were repeated at 6-monthly intervals. All side effects were carefully recorded.

Table 1 First-line Hormone Therapy

Type of hormones	*No. of patients*
Stilboestrol	4
Orchiectomy	7
LHRH agonist	11
Total	22

Table 2 Performance Status

ECOG scale	*No. of patients*
0	3
1	4
2	11
3	4

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Results

Twenty-one patients were evaluable for response, duration of response and toxicity, 1 patient having been lost to follow-up. Follow-up ranged from 6 months to 3 years (mean 22 months). Response criteria were those of the National Prostatic Cancer Project (NPCP) (Murphy and Slack, 1980).

There were no complete or partial responses. Stable disease was observed in 6 patients (28.5%) who had shown disease progression prior to commencing megestrol acetate. The duration of this response ranged from 6 to 12 months (mean 40 weeks). All of these patients had a 40 to 50% reduction in their PAP levels, but insufficient clinical or radiological response to meet the NPCP criteria for partial response. All other 15 patients experienced disease progression. Eight patients (38%) reported subjective improvement whilst on megestrol acetate with an increase in performance status by 1 or 2 points on the ECOG scale, a reduction in analgesic usage and an increase in appetite and weight gain. Six of these patients also showed stabilisation of disease as mentioned above. The toxicity of megestrol acetate was minimal. Two patients had unacceptable weight gain and another 2 experienced exacerbations of congestive cardiac failure requiring increased diuretics and a reduction in megestrol acetate to 80 mg/day.

Discussion

It has been reported that 80% of patients with prostatic carcinoma have hormonally responsive tumours (Bailar and Byar, 1970; Byar, 1973; Altwein, 1982; Schmidt, 1983). If untreated, patients with advanced metastatic disease have a poor prognosis, 69% dying within 18 months (Nesbit and Baum, 1950), and even when treated, relapse commonly occurs within 2 years (Resnick and Grayhack, 1978) with a mean survival of 1.8 years (Schoonees *et al.*, 1972; Klein, 1979) and a 50% mortality rate within 6 months (Johnson *et al.*, 1977; Paulson, 1984). Controversy exists as to whether this relapse is due to incomplete ablation of circulating androgens (Labrie *et al.*, 1983; Geller, 1985).

Di Silverio and Sciarria (1986) showed a response rate of 74.3% in patients managed with bilateral orchiectomy and cyproterone acetate, but this is similar to the results following orchiectomy or oestrogen therapy alone (VACURG, 1967; Bailar and Byar, 1970), suggesting that adrenal androgens do not exert a major influence over tumour control. This has also been demonstrated by Schultz *et al.* (1987). However, there are some patients who, having failed first-line hormonal therapy, will respond to further hormonal manipulation, as reported in the early surgical series of andrenalectomy and hypophysectomy reviewed by Brendler (1973). Similarly, medical adrenalectomy by means of aminoglutethimide produced objective response rates of 20 to 39% (Drago *et al.*, 1984; Murray and Pitt, 1985; Harnett *et al.*, 1987) and a subjective response rate of up to 75% (Rostom *et al.*, 1982; Ponder *et al.*, 1984), although toxicity was considerable, with nausea, lethargy, depression, skin rashes and confusion making it necessary to discontinue treatment in 18% of patients (Harnett *et al.*, 1987). It is possible, however, that complete andrenal suppression is not necessary, since there is evidence that hydrocortisone acetate, when used alone, suppresses adrenal androgens more effectively in relapsed patients than when combined with aminoglutethimide (Plowman *et al.*, 1987). This finding is in accord with data presented by Sciarra *et al.* (1973), who reported a reduction in adrenal androstendione levels in castrated patients managed with dexamethasone alone.

Many other agents have been used in the management of hormonally relapsed patients, including the anti-androgens cyproterone acetate and flutamide (Wein and Murphy, 1973; Stoliar and Albert, 1974; Smith *et al.*, 1979) and agents suppressing plasma testosterone such as spironolactone (Walsh and Siiteri, 1975).

All of these agents are associated with subjective patient responses varying from 39 to 74%, but objective responses are poorly documented.

Our results using megestrol acetate are comparable to those of Crombie *et al.* (1987), who reported 1 partial response and 7 stable disease states in 28 evaluable patients receiving megestrol acetete for more than 6 weeks. In our patients, megestrol acetate was very well tolerated, with minimal morbidity and an overall response rate similar to other second-line hormonal manipulations. It also has the advantage of ease of administration, using a single daily dose, and the benefit of a steroidal effect which improves both appetite and well being.

In this study of second-line hormonal therapy in advanced prostatic cancer, our results with megestrol acetate are comparable to those of other hormonal approaches. However, whether the subjective results obtained are a consequence of the anti-androgenic or steroidal effects of megestrol acetate will be determined only by a randomised study comparing megestrol acetate with low dose steroid therapy.

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Effect of High-dose Medroxyprogesterone Acetate on Plasma Hormone Levels and Pain Relief in Patients with Advanced Prostatic Cancer

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Summary—High-dose medroxyprogesterone acetate (MPA) was given orally to 7 patients with advanced prostatic cancer and severe pain due to bone metastases; 5 patients had stable and 2 had progressive disease. Pain relief was obtained in 6 patients. Two patients who reported complete relief of pain showed suppressed levels of gonadotrophins after MPA treatment. In the other patients, suppression of plasma gonadotrophin levels was observed before treatment. The plasma levels of prolactin, growth hormone and thyroid stimulating hormone were not affected by MPA. Only 1 patient showed suppression of plasma adrenocortical trophic hormone. The plasma levels of cortisol and dihydroepiandrosterone sulphate were suppressed in 6 patients, but there was no correlation between the suppression and the occurrence of pain relief. These findings suggest that the mechanism of pain relief by high-dose MPA may be very complicated.

It is often difficult to control pain in patients with multiple metastatic prostatic cancer. Various treatments have been reported (Donati *et al.*, 1966; Keen, 1980; Benson *et al.*, 1982) and high-dose medroxyprogesterone acetate (MPA) has been found to be effective in relieving pain in patients with advanced prostatic cancer (Rafla and Johnson, 1974). However, the mechanism by which this is achieved is not clearly understood. We report the effect of high-dose MPA on plasma hormone levels and pain relief in patients with advanced prostatic cancer and discuss the relationship between changes in plasma hormone levels and pain relief.

Patients and Methods

Seven patients with histologically documented carcinoma of the prostate with clinical and radiological evidence of progressive metastatic disease were studied. They were suffering from severe pain due to bone metastases. Their ages ranged from 53 to 77 years (mean 67).

All had undergone prior hormonal treatment (orchiectomy, conventional dosages of oestrogen and LH–RH analogue). They had also received at least 1 other form of treatment, usually a second hormonal manipulation, estramustine phosphate or chemotherapy. Four had received palliative radiation to painful bone metastases (Table). Each patient was treated with MPA 1200 mg orally/day.

The criteria used to evaluate the effect of treatment were in accordance with NPCP (Murphy and Slack, 1980). Pain relief was considered complete if patients reported no pain, partial if there was a reduction in pain and no change if symptoms were unrelieved.

Before and after high-dose MPA therapy, plasma hormone levels were measured. Luteinising hormone (LH), follicle stimulating hormone (FSH), prolactin (PRL), growth hormone (GH), adrenocortical trophic hormone (ACTH) and thyroid stimulating hormone (TSH) levels in plasma were determined by double-antibody radioimmunoassay methods. The plasma level of dihydroepiandrosterone sulphate (DHEA-S) was measured by dextran charcoal radioimmunoassay. The plasma cortisol level was determined by a solid phase tube

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radioimmunoassay method. Normal ranges were as follows: LH 5–30 mIU/ml; FSH 5–22 mIU/ml; PRL 2.0–20.0 ng/ml; GH <5 ng/ml; ACTH <50 pg/ml; TSH <10 µu/ml; cortisol 5.6–21.3 µg/ml; DHEA-S 400–1500 ng/ml.

Results

As shown in the Table, 5 of the 7 patients had stable and 2 had progressive disease. Pain relief was obtained about 2 weeks after treatment and in 6 cases it lasted from 2 to 8 months (average 5).

Two patients who reported complete pain relief showed suppression of LH and FSH levels in plasma after 2 weeks' treatment. In the other patients, plasma levels of LH and FSH were suppressed before treatment with MPA and this suppression continued afterwards (Figs 1A, B). Two of the 5 patients had already been treated with LH–RH analogues: 1 experienced partial pain relief and the other no relief. In 5 patients the plasma level of PRL was above normal both before and after treatment and in 2 patients it was within normal limits. No significant changes were observed (Fig. 1C). Before MPA therapy, plasma GH and TSH levels were above normal in 2 cases but all patients had normal levels after treatment (Figs 2A, B). In 4 cases the ACTH plasma level was suppressed before treatment. Only 1 patient showed suppression of plasma ACTH within 1 week of treatment and 2 did not show complete suppression (Fig. 3A). As shown in Figure 3B, 5 patients had abnormally high cortisol levels in plasma before MPA therapy but suppression was observed within 2 weeks of treatment. One patient had a normal plasma level of cortisol before the treatment and suppression was observed 3 weeks after MPA therapy. In 1 instance the plasma level of cortisol was abnormally low, but suppression was not complete after treatment. Six patients showed suppressed levels of plasma DHEA-S within 2 weeks of treatment. Before MPA therapy, the plasma level of DHEA-S was abnormally low in 1 patient who reported no pain relief, and suppression continued after treatment (Fig. 3C).

Discussion

MPA is a potent synthetic progestational steroid useful in the palliation of advanced carcinoma of the endometrium and breast. High-dose administration of MPA is considered to be more effective in prostatic cancer (Nilsson, 1982). In the management of breast cancer, high-dose MPA appears more effective than low-dose treatment and this is thought to reflect a dual mechanism: the direct action of MPA on the tumour cell and suppression of the hypothalamo-pituitary axis (Blossey *et al.*,

Table Details of Patients

Patient no.	*Age (years)*	*Previous therapy*	*Effect*	*Pain relief*	*Duration of pain relief (months)*	*Prognosis*
1	60	Hormone therapy Chemotherapy	NC	Complete	8	Alive at 14 months
2	70	Hormone therapy Chemotherapy Radiotherapy	NC	Complete	4	Died 8 months later
3	71	Hormone therapy (including LH–RH analogue) Chemotherapy	PD	Partial	3	Died 6 months later
4	53	Hormone therapy Chemotherapy Radiotherapy	NC	Partial	7	Died 12 months later
5	77	Hormone therapy Chemotherapy	NC	Partial	6	Died 10 months later
6	65	Hormone therapy Chemotherapy Radiotherapy	PD	Partial	2	Died 4 months later
7	76	Hormone therapy (including LH–RH analogue) Chemotherapy Radiotherapy	NC	No change	–	Died 4 months later

NC = No change. PD = Progressive disease.

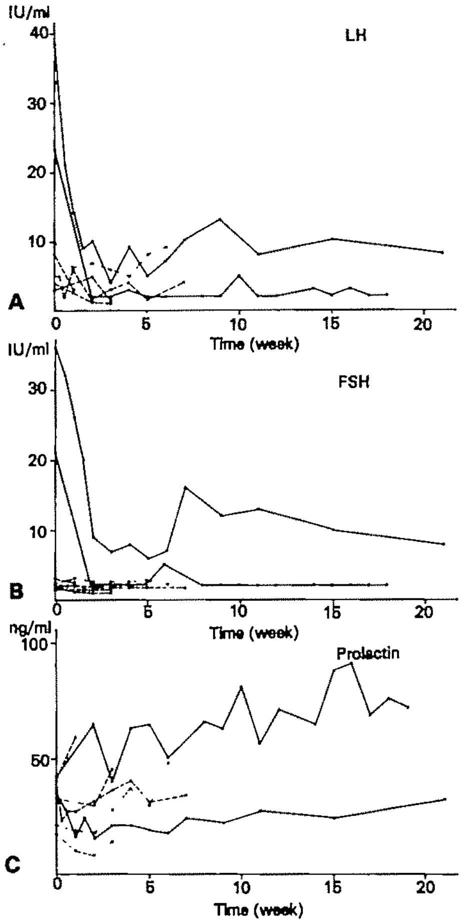

Fig. 1 Effects of high-dose MPA treatment on plasma levels of LH (A), FSH (B) and PRL (C) in patients who attained complete (———), partial (– – – –) and no (· · · ·) pain relief.

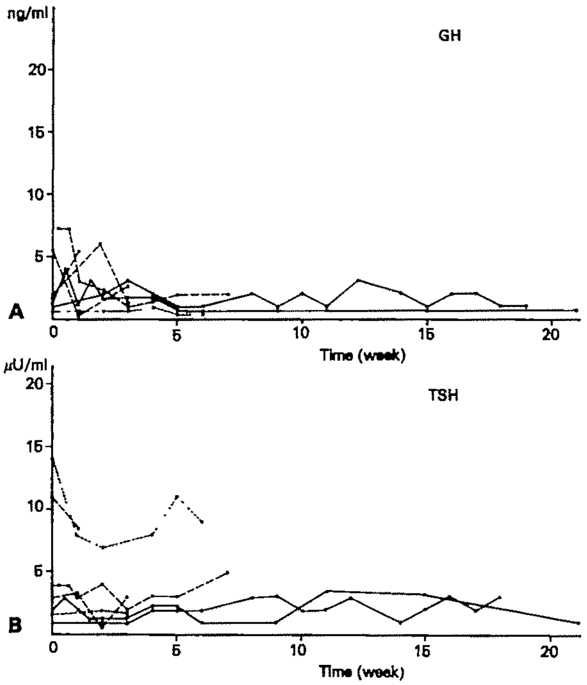

Fig. 2. Change in plasma GH (A) and TSH (B) levels after high-dose MPA therapy in patients with complete (———), partial (– – – –) and no (· · · ·) relief of pain.

1984). This mechanism may also be present in the treatment of prostatic cancer.

MPA is known to lower plasma gonadotrophin levels. The gonadotrophic function of the pituitary is more sensitive to MPA than the adrenotrophic. In this study, oral administration of 1200 mg MPA decreased both LH and FSH levels in plasma.

MPA did not interfere with the hypothalamo-pituitary-thyroid axis, an observation substantiated by the finding of normal TSH secretion, as in the present study. With respect to the thyroid, the metabolic situation of patients remained normal during treatment (Blossey *et al.*, 1984).

MPA was reported to have no effect on GH secretion in normal volunteers and patients with metastatic breast cancer (Blossey *et al.*, 1984). A similar finding was made in our prostatic cancer patients.

A close association between progression of disease and increase in plasma PRL level has been observed in patients with advanced breast cancer. After high-dose MPA treatment, the unresponsive group showed a significant increase, while the responsive group tended towards a decrease (Pannuti *et al.*, 1985). In the present study, however, the plasma level of PRL showed no significant change.

MPA has a dual mode of action on the pituitary-adrenal axis. A direct inhibitory effect on the adrenals is combined with partial inhibition of ACTH release by MPA itself or one of its metabolites (van Veelen *et al.*, 1985a). Suppression of adrenal function is more pronounced with higher doses of MPA (van Veelen *et al.*, 1985b). In this study, only 1 patient showed suppression of plasma ACTH. However, plasma levels of cortisol and DHEA-S were suppressed within 2 weeks of MPA therapy in the majority of patients.

The mechanism of pain relief by high-dose MPA remains unknown. Two of our patients who attained complete pain relief showed suppression of gonadotrophins after 2 weeks' treatment, whereas plasma gonadotrophin levels were suppressed be-

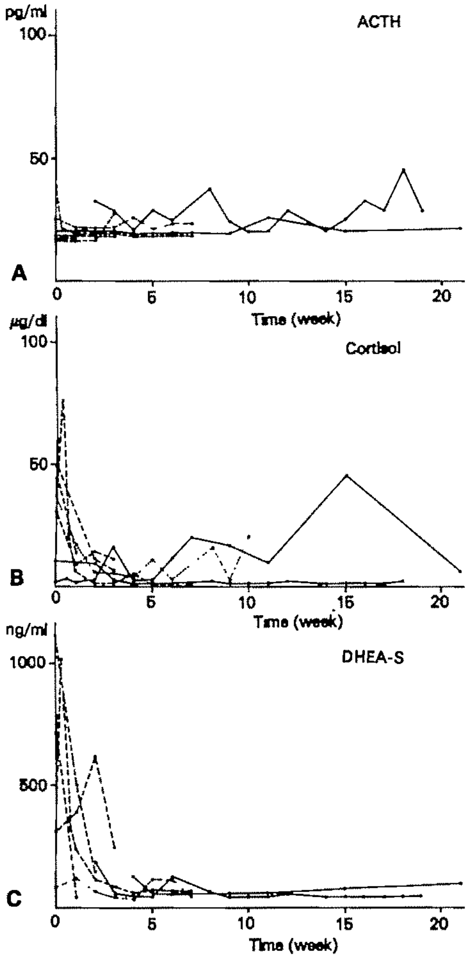

Fig. 3. Effect of high-dose MPA therapy on plasma levels of ACTH (A), cortisol (B) and DHEA-S (C) in patients with complete (———), partial (– – – –) and no (· · · ·) pain relief.

fore treatment in the other patients and 2 who had previously received LH–RH analogues did not report complete relief of pain. High-dose MPA therapy resulted in decreased levels of plasma cortisol and DHEA-S within 2 weeks, but there was no correlation between these changes and the occurrence of pain relief. According to Williams *et al.* (1980), the mechanism of pain relief by alcohol-induced pituitary adenolysis is not only related to plasma hormones but also to neurotransmitters. This means that the mechanism of pain relief by high-dose MPA may be very complicated and involve several factors other than plasma hormones.

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Effect of Parenteral Oestrogen on the Coagulation System in Patients with Prostatic Carcinoma

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Summary—Patients with prostatic carcinoma on oral oestrogen therapy have an altered coagulation system and suffer cardiovascular side effects. Oestrogens—especially oral oestrogens—are potent inducers of liver synthesised proteins, including coagulation factors.

We have assessed the effect of non-oral oestrogen on the coagulation system in patients with prostatic carcinoma. Twelve patients were given monthly intramuscular injections of 320 mg polyoestradiol phosphate (PEP). No additional oestrogens were given. No change was found in any of the coagulation factors, including factor VII, with the exception of a significant decrease in antithrombin III. No patient, including 38 patients treated with PEP, had any cardiovascular complications after a mean follow-up period of 12.9 ± 0.7 months; 76% of the patients responded to treatment.

Parenteral administration of oestrogen caused a less marked change in the coagulation system than oral administration and should be the treatment of choice for prostatic carcinoma.

Oestrogen and orchiectomy have been used for almost 5 decades in the treatment of prostatic carcinoma (Huggins and Hodges, 1941; Huggins *et al.*, 1941a, b). Adverse effects, including an increased cardiovascular mortality rate during oestrogen therapy, were reported by VACURG (1967). This led to the dosage of oestrogen being reduced but even the dosages used today are followed by an increase in the cardiovascular morbidity rate (Henriksson and Edhag, 1986). The studies which reported these adverse effects were all based on the oral administration of oestrogen.

Oral oestrogen is a potent inducer of liver synthesised proteins (Geola *et al.*, 1980). It is conceivable, therefore, that oral oestrogen may increase the formation of liver synthesised coagulation and fibrinolytic factors, which may result in an adverse coagulation profile. These changes in patients with prostatic cancer who are treated with oral oestrogen (Henriksson *et al.*, 1986) are similar to those which led to death from ischaemic heart disease in the prospective Northwick Park Heart Study by Meade *et al.* (1980). Because of the extensive first pass metabolism of oestrogens a 5- to 10-fold higher dose of oestrogen is required when given orally rather than parenterally (von Schoultz *et al.*, 1989). One way of circumventing this effect on the liver is to administer oestrogen parenterally. The aim of this study has therefore been to evaluate the effect of parenteral oestrogen on the coagulation system in patients with prostatic carcinoma.

Patients and Methods

The study group comprised 12 patients with newly diagnosed prostatic cancer who were judged by a senior urologist to be suitable for hormonal treatment. Oestrogen was given as single drug polyoestradiol phosphate 320 mg intramuscularly every month. The patients received no oral oestrogens. The cardiovascular aspects of the study were identical to those of our previous study, *i.e.* major cardiovascular events comprising myocardial function, cardiac decompensation, severe angina pectoris (medically intractable), severe intermittent claudication (requiring reconstructive surgery),

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cerebrovascular thrombosis or embolism, and thromboembolic episodes (Henriksson and Edhag, 1986). Patients who suffered a major cardiovascular event were withdrawn from oestrogen treatment and later subjected to orchiectomy.

Blood sampling was performed before and 3 months after the start of oestrogen therapy. Nine volumes of blood were drawn in vacutainer tubes containing 1 volume 0.129 M sodium citrate and immediately centrifuged at 2100 g/min for 30 min. Plasma was separated and stored in aliquots at −70°C for later analysis. Amidolytic methods using chromogenic peptide substrates (Kabi Vitrum AB, Stockholm, Sweden) were used for the analysis of the following variables: factor VII with S-2222 (Oswaldsson *et al.*, unpublished data), plasminogen (PG) with S-2251 (Friberger and Knös, 1979); antithrombin III (AT III), measured as heparin cofactor, with S-2238 (Abildgaard *et al.*, 1977); urokinase inhibiting activity (urokinase inhibitor) with S-2444 (Mettinger and Egberg, 1982); and C1-esterase inhibitor with S-2314 (Wiman and Nilsson, 1982). In addition, factor VII was also assayed by a clotting method using human plasma deficient in factor VII (Koller *et al.*, 1951). Factor VIII:C was measured by a 2-stage thrombin generation method (Savidge *et al.*, 1979).

The plasma samples were analysed against a standard curve constructed using plasma pooled from healthy normal subjects, mostly men aged 40 to 60 years. In addition, factor VIII:C values were corrected against the international WHO standard. The D dimer—a fibrinolytic degradation product of cross-linked fibrin—was measured by an ELISA method using microtitre plates and antibodies from Mabco Ltd, Springwood, Australia (Rylatt *et al.*, 1983). Fibrinogen was determined according to Vermylen *et al.* (1963). With the exception of fibrinogen and D dimer, all values were expressed as a percentage of the plasma pool.

Values before and during oestrogen treatment were compared using the *t* test for paired observations. Values are given as means ± SEM.

Results

The 12 patients in this study were a subgroup of 38 patients with prostatic cancer who were treated with monthly PEP injections in 3 different dosages (160, 240 and 320 mg). As reported previously, there were no cardiovascular complications in this group after a mean follow-up period of 12.9 ± 0.7 months and 29/38 patients responded to treatment (Henriksson *et al.*, 1988).

Table Inhibitors and Activators of Coagulation and Fibrinolysis in Patients with Prostatic Cancer before Treatment (Baseline) and during Treatment with 320 mg PEP i.m. Monthly for 3 Months

	Baseline (Mean ± SEM)	*Oestrogen (PEP) (Mean ± SEM)*
Factor VII (amidolytic method)	108 ± 6	110 ± 8
Factor VII (clotting method)	110 ± 6	110 ± 6
Factor VIII	153 ± 20	148 ± 15
Fibrinogen	4.2 ± 0.4	4.1 ± 0.7
Antithrombin III	97 ± 4	86 ± 4*
Plasminogen	108 ± 5	99 ± 5
C1 esterase inhibitor	115 ± 6	101 ± 6
Urokinase inhibitor	95 ± 4	99 ± 4*
D dimer	356 ± 196	172 ± 63

* $P < 0.01$ compared with baseline value.
Values are given as per cent of mean reference values.

As shown in Figure 1 and in the Table, there were no changes in any of the coagulation variables in patients receiving 320 mg PEP, except for a significant decrease in antithrombin III ($P = 0.007$). Factor VII analysed by the amidolytic method showed good correlation ($r = 0.85$) with the coagulation method (Koller *et al.*, 1951).

With regard to fibrinolytic factors, urokinase inhibitor increased during parenteral oestrogen therapy and plasminogen tended to decrease in patients receiving 320 mg (Fig. 2, Table). In addition, 4 of the 12 patients had increased values

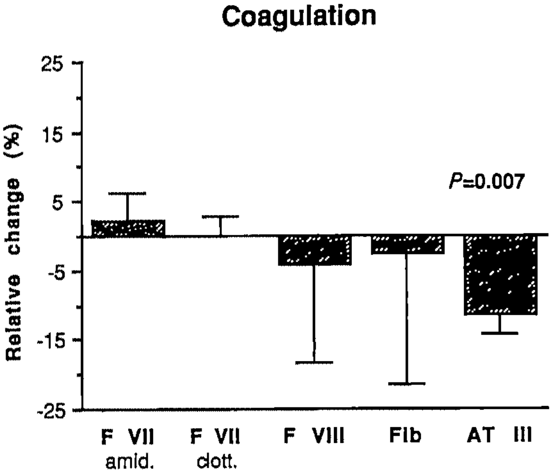

Fig. 1 Relative change (per cent) of factors VII (F VII) and VIII (F VIII), fibrinogen (Fib) and antithrombin III (AT III) in patients with prostatic cancer following parenteral administration of polyoestradiol phosphate 320 mg i.m. every month for 3 months. Mean and SEM.

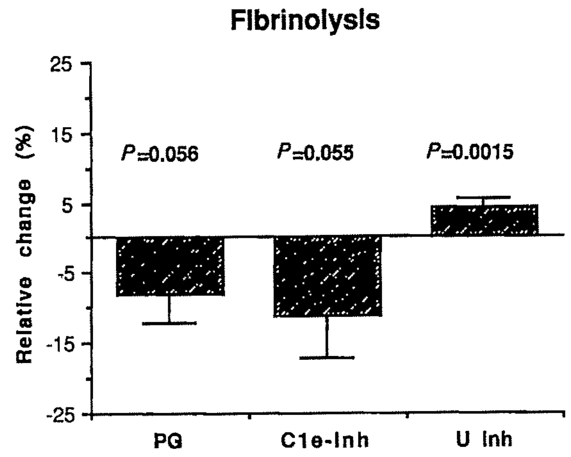

Fig. 2 Relative change (per cent) of plasminogen (PG), C1 esterase inhibitor (cle-inh) and urokinase inhibitor (U inh) in patients with prostatic cancer following parenteral administration of polyoestradiol phosphate 320 mg i.m. every month for 3 months. Mean and SEM.

of the D dimer prior to treatment compared with only 1 patient during parenteral oestrogen therapy.

Discussion

It has been shown that patients with prostatic carcinoma who are treated with parenteral oestrogen in the form of monthly intramuscular injections of PEP show no variation in coagulation factor levels except for a decrease in antithrombin III. This contrasts with oral oestrogen treatment, where the factor VII level increases (Henriksson *et al.*, 1986). The probable importance of factor VII was revealed when it proved predictive of cardiovascular events in the prospective study by Meade *et al.* (1980). Furthermore, the increase in factor VII during oral oestrogen therapy has been shown to correlate with the change in ST depression during exercise tests, *i.e.* an increased factor VII level correlated with signs of increased coronary stenosis (Henriksson *et al.*, 1989). It is therefore possible that the lack of increase in factor VII during non-oral oestrogen is beneficial for the arteries.

With regard to fibrinolysis, we found an increased level of urokinase inhibitor and a tendency to decreased plasminogen values. These changes are the opposite to those seen during oral oestrogen therapy. Furthermore, the number of patients with abnormal values of the D dimer decreased during parenteral oestrogen therapy. This is also in contrast to the findings during oral oestrogen treatment. In summary, we found a decrease in fibrinolytic capacity and activity during parenteral oestrogen treatment.

An important finding in this study was that none of the 38 patients treated with varying doses of PEP developed cardiovascular problems during the first year of treatment (Henriksson *et al.*, 1988). This contrasts with the findings in an earlier study involving oral oestrogens, when a 25% incidence of cardiovascular complications was found during the first year (Henriksson and Edhag, 1986). The baseline characteristics of the patients in both studies were comparable.

The aim of endocrine therapy for prostatic carcinoma is to achieve castrate levels of testosterone. This is possible with 320 mg PEP (Carlström *et al.*, 1989). It is thus conceivable that the influence of oestrogen on target organs (with the exception of the liver) was the same as in studies involving oral oestrogens. Because oestrogen was given parenterally, it is probable that its effect on the liver would be only a fraction of that produced by oral oestrogen (von Schoultz *et al.*, 1989). This might explain the lack of induction of liver synthesised coagulation factors. However, antithrombin III decreased in this study in the same way as it did in other studies of oestrogen treatment (Henriksson *et al.*, 1986). The decreased antithrombin III levels during parenteral administration of oestrogen might indicate a potential risk of venous thrombosis and this should be assessed in a prospective randomised study.

In conclusion, it has been shown that parenteral administration of PEP, in doses producing orchiectomy levels of testosterone, induces less pronounced changes in the coagulation system than those resulting from oral administration. The explanation for this is probably a greatly reduced effect on the liver. None of our patients has had any cardiovascular complications and parenteral rather than oral oestrogen is recommended for the treatment of prostatic carcinoma.

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Microwave Warming of 1.5% Glycine Solution

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Summary—The urological irrigating fluid 1.5% glycine is routinely warmed in specifically designed warming drawers prior to use. This study shows that the use of microwave energy to achieve body temperature in 2-litre bags of glycine solution is biochemically safe and that the sterility of the solution is maintained. There is a linear relationship between the temperature of the solution and time in the microwave oven, so allowing a simple formula to predict the correct heating time given variable ambient starting temperatures.

A 1.5% glycine solution is the most commonly used fluid in modern urological practice. It is routinely warmed to 37°C before use in large warming cabinets designed specifically for the purpose.

Microwave ovens have already been shown to be useful in the warming of crystalloid solutions, plasma, antibiotic solutions, red cell suspensions and total parenteral nutrition formulations (Sherman and Durner, 1974; Ausman and Kerkhof, 1982; Holmes *et al.*, 1982; Werwath *et al.*, 1984) but a review of the literature revealed no data on their use in warming 1.5% glycine solutions.

We describe a method of warming such solutions by microwave radiation.

Materials and Methods

All testing was performed in a single Panasonic 1.3 kW, 650 W, 2450 MHz Carousel microwave. A single 2-litre plastic polyvinyl-chloride (PVC) PL146 bag of Travenol 1.5% glycine solution was placed on the carousel after the outer opaque protective covering had been removed. Bags of solution were at a starting temperature of either 12°C or 22°C.

The digital heating time display was selected in seconds and all testing was performed at maximum output of the oven. Heating time was uninterrupted and the bags were vigorously agitated by hand at completion.

Temperatures were recorded before and after microwave treatment using 2 techniques, a telemetric probe inserted directly into the solution via the container's rubber portal and a standard glass mercury column thermometer (Dalili and Arriana, 1974).

Samples of the solution were obtained for microbiological culture after microwave treatment by puncturing a bag with a 22F gauge needle via the container's rubber portal; 5 ml of fluid were taken for each culture. Fluid was extracted in a similar fashion from the bags before and after microwave treatment to analyse for glycine concentration and potential fragments of glycine. The analyses were performed using a Waters Associates (Milford, USA) chromatograph on a Novapak C18 radially compressed column. The mobile phase consisted of 0.1% phosphoric acid, pH 2.85. Detection was by UV at 200 nm and quantitation was performed by peak area following automatic injection (20 µl) without internal standardisation. The advantage of this method is that the glycine is measured at low wavelength without the need for gradient elution, derivatisation or the addition of ion pairing reagents.

Initially, the solution was heated for variable times in order to calculate the standard time necessary to heat a bag from room to body temperature. Each measurement was repeated 5 times to increase accuracy.

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Results

The results (Fig.) represent mean temperatures obtained by the 2 different techniques following variable heating times. The variation between the methods was less than 2%.

Three minutes were required to raise room temperature glycine to body temperature. The stability and sterility of the solution were tested after heating for 3 and 6 min. The matched paired data obtained from analysis of the solutions by liquid chromatography before and after microwave treatment were compared. No statistical difference was found using the paired Student's *t* test ($P = < 0.001$), indicating that microwave heating has no measurable effect on glycine concentrations.

There is a direct linear relationship between heating time in the microwave and temperature gain of the solution. Using least squared regression analysis, lines of best fit are shown in the Figure. The correlation coefficient of these data is 0.998.

Using this information, the following equation was derived in order to predict the microwave heating time (t) to achieve the desired temperature given different starting temperatures:

$$t(\text{sec}) = (\text{Desired temp} - \text{Starting temp}) \times 360/29$$

All samples of fluid taken for microbiological culture were sterile after 2 weeks' incubation.

Discussion

The choice of a 650 W, 2450 MHz frequency microwave unit was based on availability and on previous reported problems with microwave ovens of higher wattage (Hansen, 1979). The need to shake the bag's contents vigorously after heating is based on the uneven nature of microwave heating (Staples and Griner, 1971).

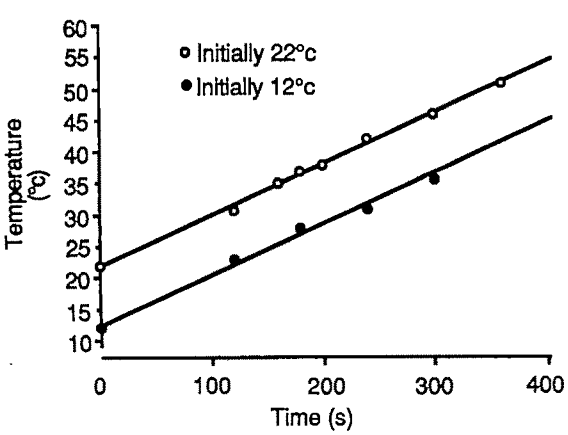

Fig. Temperatures of 2-litre bags of 1.5% glycine solution after microwave heating for various times.

The bags used are produced by Travenol. The safety of PVC PL 146 in microwaves has been described by Holmes *et al.* (1982). The outer opaque protective wrapping of the glycine bag was removed immediately prior to heating as its safety has not been established.

In our experience, timing the warming of bags before use did not pose a problem. A 2-litre bag of glycine is used every 4 to 5 min during a transurethral resection of prostate and the heating period is approximately 3 min, given a theatre temperature of 22°C. The bags are normally heated to 38°C, thus compensating for any minor cooling experienced during delivery and a potential delay in use. Our unpublished data relating to the drop in temperature of a 2-litre bag of glycine after reaching 38°C show that there is less than a 1° fall after 5 min at an ambient temperature of 22°C.

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Urethral Calculi

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Summary—We present 56 patients with urethral calculi. In males the commonest location was the posterior urethra; 46 patients complained of dysuria but urinary retention was present in only 7. In 9 patients with penile urethral calculi, 6 had associated urethral disease (urethral stricture in 5 and urethral diverticula in 1). Transurethral litholapaxy or lithotripsy after retrograde manipulation was performed in 33 patients. Endoscopic manipulation was found to be the safest procedure.

Although urethral calculi are said to be rare in the western hemisphere and fairly common in oriental countries, detailed reports are few. Urethral calculi cause dysuria or urinary retention and most patients require urgent treatment. We have reviewed the diagnosis and treatment of 56 patients with urethral calculi.

Patients and Methods

Between 1965 and 1985, 56 patients (54 males, 2 females) with urethral calculi were seen at this hospital. They ranged in age from 3 to 81 years (average 46). All except 1 were adult and 53 were over 30 years old. They were analysed with regard to location of the calculi, symptoms, associated diseases and management.

Results

The commonest site for calculi in the male was the posterior urethra (37); there were 2 in the bulbous urethra, 9 in the penile urethra and 6 at the meatus. Associated urethral disease was found in 9 patients.

Fifty-five of the 56 patients were symptomatic: dysuria (46), burning with micturition (16), gross haematuria (10), urinary retention (7) and urinary frequency (7). A urethral mass was felt in 1 patient. Sixteen male patients (29.6%) had associated diseases of the lower urinary tract (Table 1). The 2 female patients had no associated urinary pathology. Eighteen patients (32%) had associated urinary calculi (renal calculi (9), renal and ureteric calculi (3), ureteric calculi (2) and vesical calculi (4)). Ultrasound examination was performed in 5 patients and stones were identified in every case.

Management of the calculi is summarised in Table 2. In 3 cases a suprapubic procedure was performed, the indications being urethral calculus with a large vesical calculus in 2 patients and injury with a metallic sound in 1. External urethrotomy of the penile urethra was performed in 6 patients, of whom 5 had a urethral stricture and 1 had urethral diverticula.

Discussion

It is said that urethral calculi are related to hygiene and diet. The ratio of lower urinary tract calculi to upper tract calculi was 50:50 in Japan in 1945 but this is now 5:95 (Yoshida, 1979). Surveys of urinary calculi in Japan showed that urethral stones composed only 125 of 3272 cases (3.8%) in 1955 and 142 of 8187 cases (1.7%) in 1964 (Inada, 1969).

In the present series and in that of Paulk *et al.* (1976), posterior urethral calculi occurred most frequently, but Amin (1973) and Englisch (1904) reported that anterior urethral calculi were found more often. Most of the associated urethral pathology in our patients was found in the anterior urethra. Dysuria was the commonest symptom and urinary retention occurred in only 7 cases. Amin (1973) reported a high incidence of retention (88.9%) but Paulk *et al.* (1976) and Selli *et al.* (1984) found it to be an uncommon occurrence.

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Table 1 Associated Diseases of the Lower Urinary Tract in 54 Males

	No. of patients
Urethral stricture	5
Benign prostatic hypertrophy	5
Phimosis	3
Urethral diverticula	1
Neurogenic bladder	1
Following open prostatectomy	1
Total	16

Table 2 Management of Urethral Calculi in 56 Patients

	No. of patients
Posterior	
Retrograde manipulation into bladder	32
Suprapubic operation	3
Spontaneous passage	1
Refused treatment	1
Bulbous	
Retrograde manipulation into bladder	1
Spontaneous passage	1
Penile	
Urethrotomy	6
Spontaneous delivery	2
Refused treatment	1
Meatal	
Meatotomy	4
Forceps	3
Spontaneous delivery	1

In addition to routine physical examination of patients, ultrasound is also very useful in male patients. We believe that urethral calculi at any site can be identified. Associated urinary calculi were found in 32% of patients and it is important to evaluate the upper urinary tract.

The management of urethral calculi varies according to site, size and any associated lower urinary tract disease. Retrograde manipulation into the urinary bladder is the most frequent procedure for posterior urethral calculi. It is dangerous to use a metal sound or catheter to relieve acute urinary retention, although Amin (1973) recommended the use of stiff or metal catheters if a soft one failed to pass. One of our patients sustained a urethral injury during retrograde manipulation of a membranous urethral stone with a metallic sound. Blind procedures are more hazardous in patients with urethral strictures and retrograde manipulation must be used with caution. Irrigation during the endoscopic procedure expands the urethra and facilitates the return of the stone to the urinary bladder; we went on to perform litholapaxy or lithotripsy in such cases. Ultrasound lithotripsy is to be recommended. In our patients most of the anterior urethral calculi were associated with urethral disease and urethrotomy of the penile urethra was performed in 6 patients. It is dangerous to attempt to milk out the anterior urethral calculi or extract them with forceps because of potential damage to the urethral mucosa. Suarez (1985) reported that a urethral calculus could be engaged in the basket and pulled inside the urethroscope sheath, so that the stone, basket and sheath could be removed under direct vision. Endoscopic manipulation is the safest procedure and associated lower urinary tract pathology should be treated in order to prevent stone recurrence.

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Management of the Contralateral Testis in Patients with Testicular Germ Cell Cancer

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Summary—Patients with testicular germ cell tumours (TGCT) are at increased risk of developing a tumour in the contralateral testis. Such a tumour may be preceded by carcinoma *in situ* (CIS), which is more common in patients with infertility, atrophic testis or a history of cryptorchism. Of 1219 patients with TGCT seen at the Royal Marsden Hospital between 1962 and 1984 in whom the contralateral testis was managed by surveillance, 38 (3.1%) developed a second tumour and 8 died of germ cell tumours. Seventeen of 26 assessable patients (65%) exhibited at least one of the known aetiological risk factors for carcinoma *in situ*. Diagnosis of carcinoma *in situ* may lead to more appropriate management of the contralateral testis.

Patients with a testicular germ cell tumour have an increased risk of developing a second tumour in the contralateral testis (Pugh, 1976). Skakkebaek (1972) described 2 cases of infertile men who developed embryonal carcinoma of the testis where earlier testicular biopsy had shown carcinoma *in situ*. Subsequently, Berthelson *et al.* (1980) showed that testicular tumour patients with a history of infertility, cryptorchism or an atrophic contralateral testis had an increased risk of having CIS in the contralateral testis. At a later follow-up, von der Maase *et al.* (1986) showed that 36% of 19 testicular tumour patients with biopsy proven CIS in the contralateral testis developed a second testicular cancer, whereas none of 473 patients without this finding did. The group concluded that CIS was pre-malignant and that patients with testicular tumour should routinely have biopsy of the contralateral testis to diagnose carcinoma *in situ*. Patients could then be treated with low dose testicular radiotherapy (von der Maase *et al.*, 1987), which abolishes germinal epithelium and CIS whilst preserving Leydig cell function and therefore endogenous testosterone production (Rowley *et al.*, 1974). In the Royal Marsden Hospital Testicular Tumour Unit, those patients treated with radiotherapy have had the contralateral testis shielded to preserve fertility (Smithers *et al.*, 1973). However, second tumours do occur in about 3% of patients (Sokal *et al.*, 1980). The Christie Hospital technique in Manchester included the contralateral testis in the radiotherapy field, which resulted in all patients being infertile, but no second tumours occurred (Read *et al.*, 1983; Read, 1987). Careful follow-up of all patients in our unit has always included regular examination of the contralateral testis, with investigation and surgical exploration if any suspicious abnormalities are detected.

We have reviewed the case records of all patients seen between 1962 and 1984 to assess which patients who developed a second tumour would have been recognised as being at risk according to the known predisposing factors. We also assessed the advantages and disadvantages of the policy of careful surveillance of the contralateral testis.

Patients and Methods

The case notes of 1219 patients with testicular germ cell tumours were reviewed. The "value" of post-treatment fertility was assessed by the number of pregnancies produced in this group. Those patients who developed a second tumour in the contralateral testis were reviewed to see who could have been recognised previously as being at risk according to

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the proposed risk factors of infertility, an atrophic testis or a history of cryptorchism. In addition, the stage at presentation of the second tumour, together with treatment required and the eventual outcome, were determined for each patient. Since all second tumour patients underwent a second orchiectomy, they required testosterone replacement. The 2 methods available of daily tablets of Restandol or intermittent depot injections of Primoteston Depot 250 mg every 4 weeks were compared and the acceptability to the patients assessed, by interview and by a written questionnaire.

Results

After treatment, 148 of 1219 patients produced 175 pregnancies with 161 live births. This gives a fertility rate of at least 12.1%.

Thirty-eight patients (3.1%) subsequently developed a contralateral testicular tumour an average of 4.7 years after the first tumour (range 6 months–14 years). None of these patients produced a pregnancy after the first testicular tumour. The stage at presentation of the second tumour, using the Royal Marsden Hospital staging system for testicular tumours (Peckham, 1981), is shown in Table 1. The types of treatment these patients received is shown in Table 2. The histopathological diagnosis of the second tumour was compared with that of the first. There were 19 patients with a different histological type and 19 patients where both tumours were either both seminoma or both non-seminoma types. The outcome was assessed in 34 patients (89.5%); 4 were lost to follow-up. Twenty-six patients were alive and disease-free with an average follow-up of 7 years (range 4–24); 8 patients (21%) died an average of 1.7 years after diagnosis of the second tumour (range 9 months–3 years). One patient died following relapse of the more aggressive first tumour; the other 7 died from the second testicular tumour or its treatment.

Table 1 Stage at Diagnosis of Second Tumour in Patients with Bilateral Testicular Tumours

Stage	*No. of patients*
I	31
II	2
III	3
IV	2

Table 2 Management of Second Tumour in Patients with Bilateral Testicular Tumours

Treatment after orchiectomy	*No. of patients*
Surveillance	19
Radiotherapy	10
Chemotherapy	7
Combined radiotherapy and chemotherapy	2

In only 26 of the 38 patients with second tumours (68%) was there sufficient information in the case notes to assess completely whether they had had any of the proposed risk factors that might have suggested they were at increased risk of carcinoma *in situ* in the remaining testis (Table 3). Only 2 patients were noted at admission for their first tumour to have an atrophic contralateral testis; 12 of 31 patients (39%) gave a history of cryptorchism; 7 were known to be azoospermic after treatment for the first tumour. No patient who developed a second tumour fathered a child after the first tumour was diagnosed. Thus 17 of 26 patients assessed (65%) definitely had at least 1 of the risk factors and 9 patients (34%) definitely had none.

Testosterone replacement was assessed prospectively by interview of 20 men. There was considerable variation in personal preference for either oral testosterone tablets or monthly depot injections. The daily tablets produced a low and, in many cases, unsatisfactory libido. The depot injections gave a good initial libido but this decreased during the month and some patients used oral testosterone tablets as a supplement. Thirteen patients (65%) experienced troublesome hot flushes or excessive sweating and 12 (60%) found that their sex life was unsatisfactory. Some patients disliked the constant level of libido that replacement tended to produce rather than one following natural variation. Although the depot injections were inconvenient, requiring an out-patient visit, this tended to produce the most acceptable libido and was generally preferred. However, no patient felt replacement was better than normal endogenous testosterone.

Discussion

The characteristic atypical germ cells forming

Table 3 Prevalence of Known Risk Factors in 38 Patients with Second Testicular Tumours

Risk factors	*No. evaluable*	*No. with risk factor (%)*
History of cryptorchism	31	13 (39)
Atrophic testis	2	2 (100)
Infertility	16	7 (44)
At least 1 factor	26	17 (65)

carcinoma *in situ* are well recognised adjacent to germ cell tumours of the testis (Skakkebaek, 1972). The existence of this lesion and its significance in the tumour-free testis have only recently been investigated (Figs 1 and 2). The presence of CIS in the contralateral testis in 5% of testicular tumour patients (Berthelsen *et al.*, 1980) corresponds with the observed rate of second testicular tumours. Of 500 patients studied in Copenhagen by biopsy of the contralateral testis at the time of orchiectomy for TGCT, 38% of 27 patients with carcinoma *in situ* developed second tumours, but none of the 473 patients without carcinoma *in situ* developed second tumours (von der Maase *et al.*, 1986).

After orchiectomy for TGCT, careful surveillance of the contralateral testis to watch for the development of a second tumour is not ideal. Of the 38 patients in the present series who developed a second tumour, 7 (18.4%) were stage II or greater at diagnosis. Radical orchiectomy was performed in all patients, resulting in castration of young men and the subsequent need for testosterone replacement. Nineteen patients (50%) required only surveillance after orchiectomy, 10 (26%) were treated with radiotherapy, 7 (18.4%) with chemotherapy and 2 (6%) with both modalities. Each treatment involved regular hospital attendance by patients as well as more specific side effects. Despite intensive treatment, 7 patients (18.4%) died as a result of the second tumour, although 5 of these died before the introduction of effective chemotherapy in 1977; of the remaining 2 patients, 1 died from bleomycin lung toxicity. Although treatment regimes have improved over the last 2 decades, the risk of uncontrollable disease is still present. Patients who are cured of their second tumour face a lifetime of testosterone replacement. Many of the men we interviewed found the replacement therapy unsatisfactory.

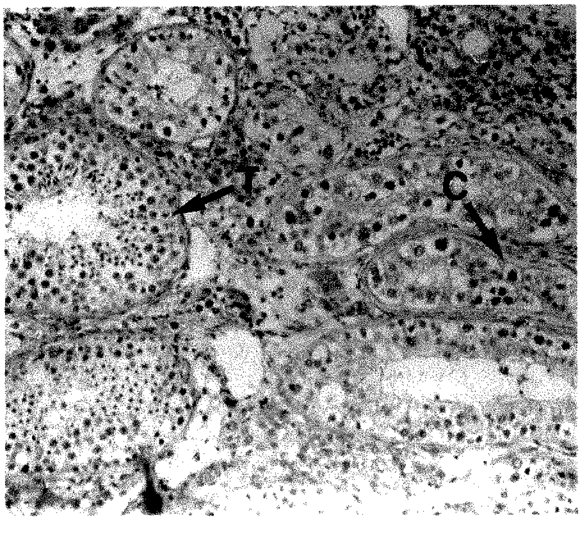

Fig. 1 Normal seminiferous tubules (T) are shown adjacent to abnormal tubules (C) which have large vocuolated carcinoma *in situ* cells between the basement membrane and Sertoli cells. (H and E ×60).

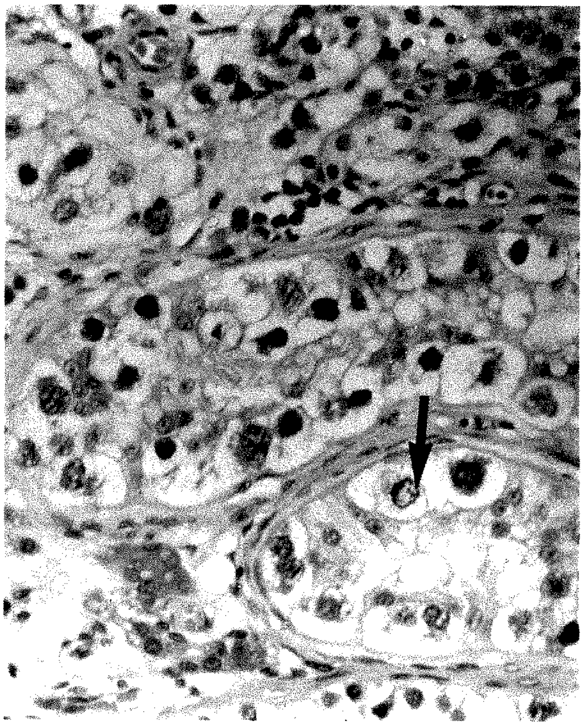

Fig. 2 Higher power magnification showing carcinoma *in situ* cells within tubule. (H and E × 120).

In the report by von der Maase *et al.* (1986), 8 patients with an initial biopsy of the contralateral testis showing CIS had intensive chemotherapy for the primary germ cell tumour and at follow-up biopsy no CIS was detected. Effective chemotherapy may be an adequate treatment for CIS, but with modern chemotherapy the germ cells may regenerate and the risk of later CIS could remain. Relatively low dose testicular radiotherapy (20 Gy) is sufficient to destroy the testicular germ cells and eradicate any CIS. The major advantage of this low dose is that Leydig cell function is preserved and therefore endogenous testosterone production is not affected (von der Maase *et al.*, 1987). The long-term control of CIS by radiation to a slightly higher dose is suggested by experience from the Christie Hospital of routine irradiation of the contralateral testis in patients with stage I seminoma. No second testicular tumours were seen (Read, 1987). CIS usually occurs in infertile patients and thus the question of radiation-induced sterility may not arise.

According to von der Maase *et al.* (1986), it seems that biopsy of the contralateral testis will give information about the chance of future development of a second testicular germ cell tumour. Should all patients having orchiectomy for their first germ cell tumour undergo biopsy? At a time when the patient is adjusting to diagnosis and treatment of a malignancy, a further surgical procedure may not be easily accepted. Since at least one-third of patients had no known risk factors for carcinoma *in situ* and would thus have been missed by a selective policy, all patients would require biopsy to avoid missing those with pre-malignant changes.

Two methods for identifying CIS cells in semen have recently been reported (Giwercman, 1988a, b). In the first, a monoclonal antibody specific for CIS cells is used to identify them microscopically in semen. The second method uses flow cytometric analysis of the DNA content of cells in semen. An aneuploid cell population has been identified in some patients with biopsy-proven carcinoma *in situ* which was not present following orchiectomy or local irradiation. These methods may provide a less invasive method for assessment of carcinoma *in situ.*

Our policy, in line with the MRC Testicular Subgroup Trial, is to biopsy the contralateral testis in patients with infertility, testicular atrophy (*i.e.* volume ≤ 12 ml) or a history of maldescent and in addition to recommend regular careful follow-up and self-examination of the remaining testis by the patients. Those who are found to have CIS are offered randomisation between radiotherapy or observation.

Acknowledgement

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Sperm Morphological Analysis: Comparison of Two Methods in Human Semen

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Summary—Sperm morphological analysis was performed by 2 methods: light microscopy on Papanicolaou stained material and scanning electron microscopy. Both methods were found to have acceptably low levels of observer error and a positive correlation existed between them. Sperm morphology was analysed by both methods in 2 groups: (1) 104 proven "fertile" men, husbands of women who had just given birth and whose paternity had been proven by HLA studies with >95.5% certainty; (2) 53 infertile men from primary infertile marriages in whom no female cause could be found and excluding those with azoospermia. There was no statistically significant difference in medians between the 2 groups when sperm morphology was analysed by light microscopy, but analysis by scanning electron microscopy did show a significant difference.

Controversy has continued over the importance of sperm morphology since Williams and Savage (1925) reported a high correlation between the breeding record of bulls and the morphology of their spermatozoa. These authors concluded that "morphology of the head of the sperm constitutes the greatest single source of information as to the fitness of the cells for reproduction". Moench and Holt (1930) applied this type of study to the human and were even more specific in their conclusion: "that when the number of abnormal forms is above 25% there is always sterility". Others have echoed this view. Lane-Roberts *et al.* (1939) stated "that no man whose reproductive record could be regarded as satisfactory produced more than 18% of spermatozoa with abnormal head forms".

Different results were obtained by Hotchkiss *et al.* (1938) in their study of 200 men whose wives were delivered of normal children. In their series, 2.5% had more than 25% abnormal forms. MacLeod and Gold (1951) studied 874 men whose wives were pregnant at the time of the study and found that 39% had more than 20% abnormal forms, 17% had more than 30% and 3% more than 50% abnormal forms. Falk and Kaufman (1950) found that in 100 fertile men the mean percentage of completely normal forms was 88.4%.

Human semen differs from that of bull, ram and guinea pig in having a relatively high natural variation in shape of normal spermatozoa which makes it difficult to establish which forms are associated with infertility and which are normal variants (Freund, 1968; Hargreave and Nilsson, 1983). Freund laid down helpful standards for morphological analysis.

The constancy of morphological distribution of an individual's spermatozoa in different ejaculates has been emphasised by MacLeod and Gold (1951) but Freund (1968) has challenged this.

Several stains have been used to facilitate the examination of the morphological characteristics of semen. Papanicolaou's stain (MacLeod and Gold, 1951; MacLeod, 1964; Eliasson, 1975) is thought to define the fine detail of sperm morphology and immature forms very well, although Meyer's haematoxylin method is easier and needs fewer stages. Jager *et al.* (1984) compared supravital staining of human spermatozoa using trypan blue and eosin; trypan blue had the advantage of showing the presence or absence of the acrosome and may detect cytotoxic antibodies.

Scanning electron microscopy has seldom been used in the study of semen morphology. Lacy *et al.* (1974) used cells fixed in glutaraldehyde, concentrated by low speed centrifugation, dried with acetone, collected on a millipore filter and coated

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with gold. Up to 40 spermatozoa per field were suitable for assessing variations in general shape and size; at higher magnification, differences in surface texture could be examined more critically. In the analysis of semen this should be more useful than transmission electron microscopy, which is too difficult and expensive a technique to be of general use. Liakatas *et al.* (1982) scored the morphological abnormalities that could be seen with the scanning electron microscope in 20 infertile men with and without a varicocele, paying special attention to abnormalities of the head, midpiece and tail.

To date nobody has compared sperm morphology using scanning electron microscopy with other semen measurements, including light microscopy. The predictive value of sperm morphology by both methods needs to be analysed.

Methods and Materials

Sperm morphology was analysed by 2 methods: (1) light microscopy analysis of spermatozoa stained by Papanicolaou's method and (2) scanning electron microscopy.

Light microscopy analysis of spermatozoa stained by Papanicolaou's method

A drop of fresh well mixed semen was placed on to a clean glass microscope slide and a film produced by spreading. Immediate wet fixation of the specimen was performed in a solution of 3% acetic acid and 95% alcohol. The wet fixed preparation was stained by the method of Papanicolaou (1942). The stained slide preparation was examined under oil immersion using a ×40 objective with phase contrast light microscope (Wild); 100 spermatozoa were counted and scores for head, midpiece and tail normality and abnormality, together with immature forms, were categorised according to the method described by Liakatas *et al.* (1982).

Analysis of spermatozoa morphology by scanning electron microscopy (SEM)

100 μl fresh well mixed semen were pipetted into a plastic test tube and wet fixed with 200 μl glutaraldehyde solution for 30 min. A fixed specimen was washed with phosphate buffered saline and centrifuged for 10 min at 2000 rev/min. The supernatant was discarded and the cell pellet spun-washed twice in distilled water at 2000 rev/min for 10 min and the supernatant discarded. The cell pellet was resuspended in 100 μl distilled water and a drop spread over a clean ground glass coverslip that had previously been attached to a scanning electron microscope (SEM) stub with double-sided adhesive tape; this was allowed to dry. The air dried specimen was coated with a gold film to improve electrical conduction. Coating was performed using a sputter coater to a thickness of 40 nm (Polaron E5100 SEM Coating unit). The preparations were examined with an ISI Alpha 9 scanning electron microscope. A magnification of ×2000 generally allowed examination of approximately 5 spermatozoa/field. More than 10/field made evaluation difficult; 100 spermatozoa were counted and scores for head, midpiece and tail normality and abnormality, together with immature forms, were categorised according to the method described by Liakatas *et al.* (1982).

Experiment 1—To determine the relative accuracy of a relationship between the 2 morphological methods

Five well mixed semen samples, specimens I, III and IV from pre-vasectomy patients and specimens II and V from patients attending the Infertility Clinic, were each divided into 5 aliquots to give 25 individual specimens. These were randomly numbered 1 to 25 and each independently analysed by light microscopy after Papanicolaou staining by an experienced observer (P.R.E.) and by scanning electron microscopy (A.G.).

Experiment 2—To assess the predictive value of the 2 morphological methods in determining fertile state

Two populations of men were studied, a "fertile" and an "infertile" group. The fertile group (n = 104) consisted of the partners of females in the postnatal ward of the London Hospital whose paternity had been proven with >95.5% certainty based on HLA-A, B and C antigen studies carried out on cord (child), maternal and paternal blood. All were conceived within 2 years of unprotected sexual intercourse (mean 4.8 months, SD 5.6).

The infertile group (n = 53) consisted of males from a primary infertile partnership in which there was no demonstrable female cause for infertility (based on studies to prove normal and tubal ovulation patency). Those with azoospermia were excluded. In both groups a single specimen of semen was produced by masturbation into a sterile plastic container whilst the subject was physically well following 3 days of sexual abstinence and submitted to the laboratory within 2 h of production. The semen samples were analysed for sperm morphology variation by the same methods as in Part 1.

Results

Part 1

The code was broken for the 25 specimens. For both methods the standard deviations for each of the 5 samples were determined for normal spermatozoa (Table 1). For each method of analysis, standard deviations within a single specimen were low, indicating little observer error. There was positive correlation (r = 0.7) when the mean values of the percentage of completely normal spermatozoa, estimated by the 2 techniques, were compared. It was clear that scanning electron microscopy detected more "abnormal" spermatozoa than light microscopy.

Table 1 Comparison of Light Microscopy of Papanicolaou Stained Preparations with Scanning Electron Microscopy

	Percentage completely normal spermatozoa					
Specimen	*Scanning electron microscopy*			*Light microscopy*		
	46			60		
	41	Mean	SD	72	Mean	SD
I	54	48	8.3	80	69.6	7.4
	40			70		
	59			66		
	13			30		
	17	Mean	SD	32	Mean	SD
II	18	21.2	7.9	30	29	2.6
	25			25		
	33			28		
	20			76		
	26	Mean	SD	65	Mean	SD
III	37	23	9.3	57	63.6	7.5
	20			60		
	12			60		
	45			54		
	34	Mean	SD	65	Mean	SD
IV	38	40.8	5.0	79	65	9.0
	46			63		
	41			65		
	21			45		
	31	Mean	SD	54	Mean	SD
V	29	25	4.6	45	52.4	7.1
	23			58		
	21			60		

Part 2

The Mann-Whitney U test was applied to the data; a statistically significant difference in medians and means between the 2 groups was found using scanning electron microscopy when comparing the percentage of completely normal spermatozoa. No such difference was found for the percentage of completely normal spermatozoa or other morphological scores by light microscopy. There were significant differences between the 2 groups in the variability for percentage of normal heads, tails, immature forms and normal spermatozoa scored by light microscopy and also percentage of normal heads, midpieces, tails and immature forms and percentage of completely normal spermatozoa on scanning electron microscopy.

A stepwise discriminant analysis (Computer program BMD P7M) (Dixon, 1985) was used to see how effectively these 2 methods could predict fertile from infertile and *vice versa*. The results are presented in Table 2 and show that when the percentage of completely normal spermatozoa was scored by light microscopy, an overall accuracy rate of 60% was obtained at optimal cut-off, whereas when completely normal spermatozoa were scored by scanning electron microscopy, an overall accuracy rate of 80% was obtained at optimal cut-off. The Figure shows both the true positive rate and false positive rate for the 2 methods at different cut-off points. To be of diagnostic value the test should approach a false positive rate of 0 while maintaining a true positive rate of 100%. In practice, no biological tests achieve this degree of accuracy. The ideal curve should be close to the top left hand corner. The curve for light microscopy is clearly far from this ideal, whereas that for scanning electron microscopy approximates more closely.

Table 2 Results of Discriminant Analysis to Determine Correct Classification at Optimal Cut-off

Measurement	*% Accuracy of discrimination between fertile and infertile*	*% Of fertile group that would be wrongly classified as infertile*	*% Of infertile group that would be wrongly classified as fertile*
% Normal spermatozoa by SEM	80	15	33
% Normal spermatozoa by light microscopy on Papapanicolaou	60	34	44

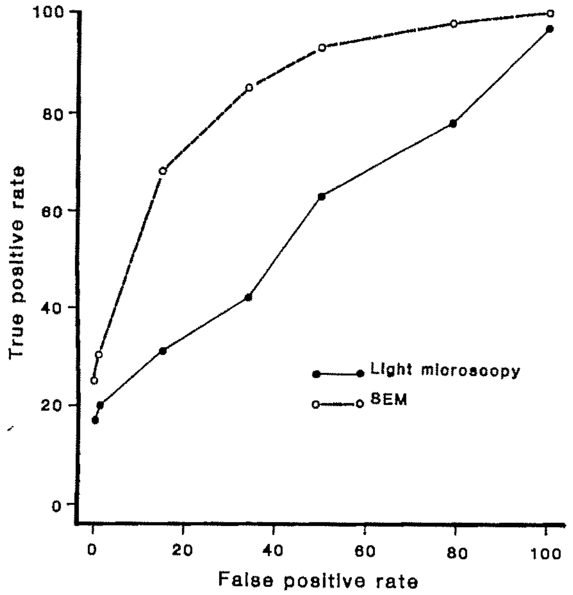

Fig. Receiver operating characteristic curve for morphology scores.

Discussion

Jequier and Ukombe (1983) emphasised the errors inherent in morphological analysis of human semen by light microscopy and showed coefficients of variation as high as 40% for the same sample. The first part of our study shows morphological analysis by both light microscopy on Papanicolaou stained preparations and scanning electron microscopy preparations to have acceptably low levels of observer error when carried out by 2 experienced observers. However, the value of light microscopy analysis as a means of predicting fertile state must be questioned in the light of our findings: no statistically significant difference was found between the medians or means for the percentage of completely normal spermatozoa as judged by light microscopy, and light microscopy analysis failed to discriminate with any degree of accuracy between fertile and infertile, even at an optimum cut-off point. Although scanning electron microscopy does give reasonably accurate discrimination between our fertile and infertile groups, it remains a time-consuming and expensive procedure and cannot be recommended for routine laboratory purposes. It is recommended that sperm morphology scores by light microscopy should be abandoned as part of "routine" semen analysis.

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Case Reports

Complete Testicular Feminisation Syndrome in Three Sisters

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Testicular feminisation syndrome is the most common cause of male pseudohermaphroditism. The underlying pathology is an end organ resistance to androgen stimulation. The main clinical features are female external development, including secondary sex characteristics, the presence of testes in the labia majora or in the inguinal canals or intra-abdominally, and the absence of internal female genitalia.

Case Report

A 19-year-old girl presented to the Endocrinology Clinic with primary amenorrhoea. On examination she had the appearance of a normal female; the breasts were well formed, pubic and axillary hair was scanty and female external genitalia were normal (Fig. 1). Suspicion was aroused when mobile hard masses were palpated in both inguinal regions.

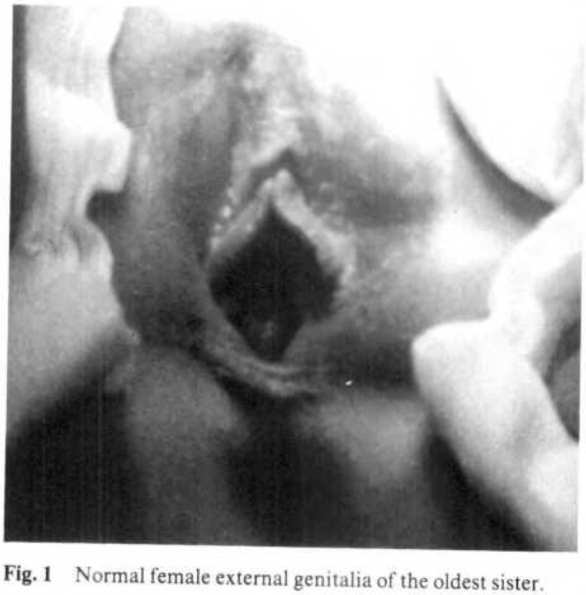

Fig. 1 Normal female external genitalia of the oldest sister.

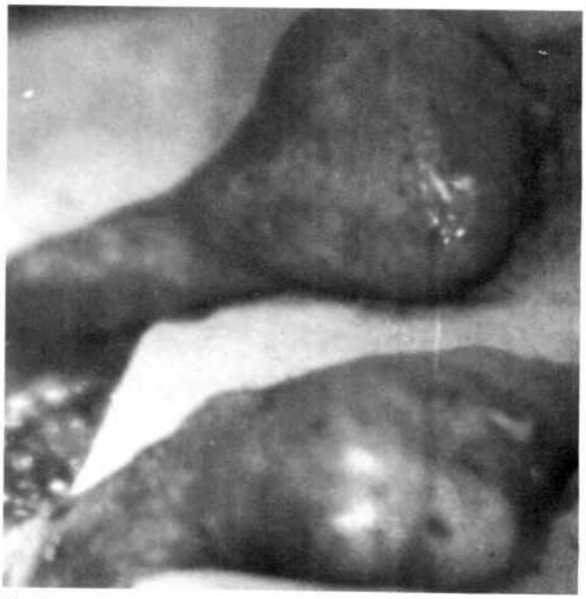

Fig. 2 Both testes after removal from the inguinal regions.

The plasma testosterone level was 390 ng/dl and the pituitary hormones were LH 19 mIU/ml, FSH 14 mIU/ml, prolactin 3 ng/ml. Oestradiol was 60 pg/ml. The karyotype was 46XY and a diagnosis of complete testicular feminisation syndrome was made.

During surgery the absence of internal female genitalia was verified and a bilateral orchiectomy was performed (Fig. 2). The patient's 2 younger sisters, aged 18 and 16 years, were also investigated. A similar diagnosis was made and similar therapeutic procedures were followed.

In the oldest of the 3 sisters plastic surgery has been performed to enlarge the vagina in order to permit sexual intercourse.

Comment

All patients with this syndrome should be brought up as females.

Although testicular tumours have been described in patients with this syndrome (Manuel *et al.*, 1976), the ideal time for orchiectomy is the early post-pubertal period, since the testes provide the hormones necessary for the development of secondary sex characteristics. We operated on the oldest girl at the age of 19, the second one at the age of 18 and waited 2 years before operating on the youngest sister, who was only 16 at the time of the initial diagnosis.

If we remove the testes before puberty, and this may happen as a result of trauma, torsion or pain, then oestrogen supplementation may become necessary (Rajfer, 1986).

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Malignant Hypertension due to Renal Carcinoma

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Renal carcinoma is seldom associated with hypertension and rarely presents as malignant hypertension. We report a case in which malignant hypertension and an abdominal bruit were the presenting features of renal carcinoma, and nephrectomy resulted in a return to normal blood pressure.

Case Report

A 49-year-old housewife presented with severe headaches and no other symptoms. On examination, blood pressure was 240/140 mmHg, pulse 120/min and no signs of failure. Retinoscopy revealed grade IV(Keith-Wagner) hypertensive changes with bilateral papilloedema. No abdominal mass was palpable but there was a soft abdominal bruit.

Full blood count, urea and electrolytes were normal. Urine analysis revealed mixed growth, no red cells, no casts and metanephrines not raised. Abdominal ultrasound, intravenous urography and CT scan confirmed a solid tumour arising from the lateral aspect of the right kidney with no spread. Renal embolisation was not possible but arteriography showed a highly vascular tumour and radical nephrectomy was performed. Histopathology described an 8-cm, well differentiated, clear cell renal carcinoma. After operation the patient remained normotensive without medication.

Comment

Renal carcinoma is recognised to be associated with hypertension. Malignant hypertension has, however, been reported in only 2 previous cases in the English literature. One was a 42-year-old woman presenting with malignant hypertension (Lebel *et al.*, 1977) and found to have an acidophilic renal adenocarcinoma. Renin levels were raised in the tumour and surrounding kidney tissue. The other case was a 14-year-old girl presenting with malignant hypertension and a facial palsy (Lindop *et al.*, 1986) and found to have a renin-secreting renal carcinoma. Suggested mechanisms in the aetiology of hypertension include renal artery stenosis, arteriovenous fistulae, renin secretion by tumour cells and ischaemia of the renal parenchyma adjacent to the tumour.

Acknowledgement

I thank Dr H. M. Leather for his permission and assistance in preparing this report.

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Crohn's Disease Mimicking Primary Bladder Tumour

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Case Report

A 17-year-old female presented with vague right iliac fossa pain which had been present intermittently for 18 months and also a history of recurrent urinary tract infections. Intravenous urography revealed hold-up in the right ureter with a mass projecting into the bladder (Fig. 1). Computed tomography showed the mass to be closely related to the right side of the bladder (Fig. 2).

Cystoscopy confirmed a huge mass on the right lateral wall which looked like an invasive tumour. Biopsy reported inflammatory cells only, with no evidence of malignancy. Subsequent laparotomy revealed extensive Crohn's disease of the caecum closely adherent to the

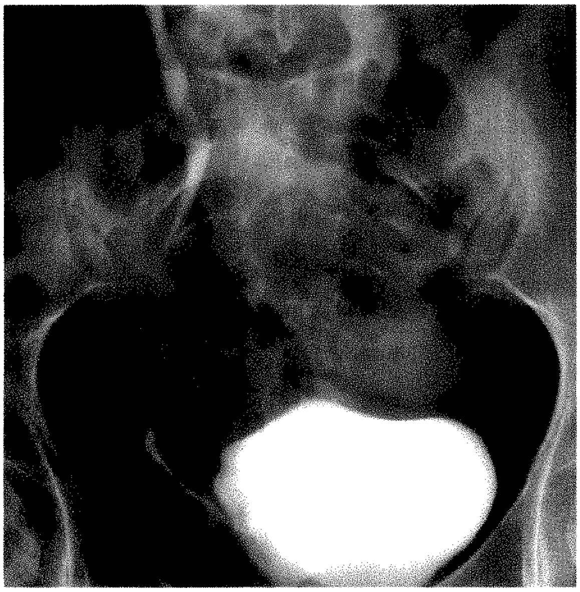

Fig. 1 IVU showing ureteric hold-up related to a right bladder wall mass.

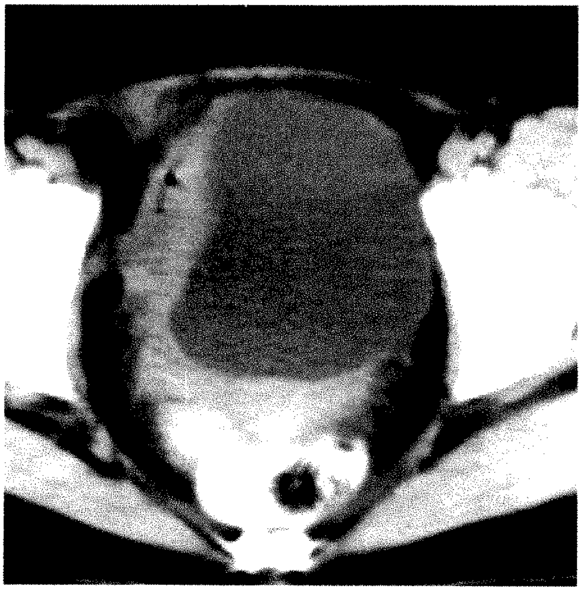

Fig. 2 Computed tomogram confirming the soft tissue mass involving the right bladder wall.

bladder and this was confirmed by histology after a right hemicolectomy was performed.

Comment

It is well known that Crohn's disease may involve the urinary tract and may present on cystoscopy as a mass lesion (Goldstein *et al.*, 1971), but roentgenographic features mimicking a primary bladder tumour have only rarely been reported (Gray and Newman, 1957; Joffe, 1976). There have been no previous reports of the CT findings.

Both surgeons and radiologists should be aware that the inflammatory changes of Crohn's disease can closely resemble bladder tumours on both cystoscopy and imaging. This case illustrates the need for caution in the application of the commonly held view that the demonstration of a solid mass lesion protruding into the bladder lumen is pathognomic of a bladder neoplasm. Awareness of this may avoid an erroneous diagnosis and allow consideration of alternative pathology, especially in younger patients.

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Asymmetrical Bilateral Genital Ureteric Ectopy

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Case Report

K.G. a 16-year-old white female, was referred because of continuous leakage of urine despite a history of otherwise normal voiding. She denied any stress incontinence or urgency.

At the age of 4 years the diagnosis of complete duplication of the left ureter with an ectopic ureteric opening in the introitus was made and a left upper pole nephrectomy was performed. Despite this procedure she remained wet and a year later vesicoureteric reflux on the right was diagnosed and a right ureteric reimplantation was performed together with removal of the left upper pole ureteric remnant. The patient remained incontinent and 2 years later a bladder neck lengthening procedure was carried out because of a patulous urethra. The patient still remained wet, using approximately 12 pads per day, and at the age of 16 was referred for evaluation and further treatment.

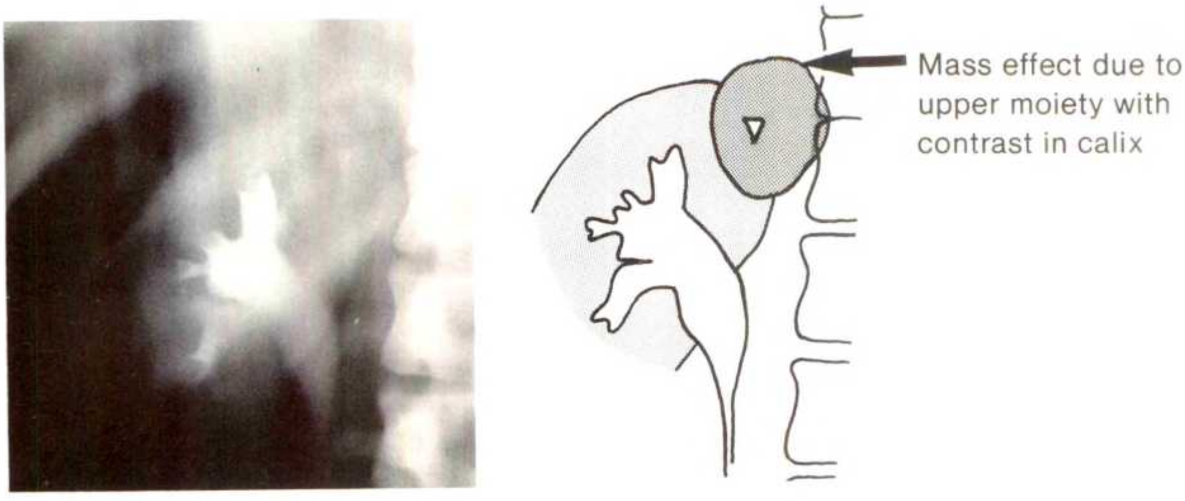

Fig. 8 cm tomogram from IVU.

On physical examination nothing abnormal was found. Urine microscopy and culture were negative. On reviewing the IVU, which had been performed elsewhere and reported as normal except for the previous left heminephrectomy, features suggesting a right-sided duplication, with a small upper pole moiety, were noted on the tomograms only (Fig.). At cystoscopy, both left- and right-sided ureteric openings near the bladder neck were identified; no extra or ectopic opening was found despite careful inspection of the introitus and vaginoscopy.

At exploration a double right ureter was identified with a dilated upper pole ureter being followed to its ectopic insertion into the uterine cervix. An upper pole nephroureterectomy was performed. The patient recovered well and is now dry.

Comment

Ectopic ureter is a rare anomaly which seems to be commoner in females, although this may be partly due to the fact that incontinence is not a feature in males, thus making clinical recognition more difficult. More than 80% of ectopic ureters in females are associated with duplicated collecting systems (Perlmutter *et al*., 1986). Although contralateral duplication is common, being reported in almost 50% of cases, bilateral ectopic ureters are less common and occur in only about 7% of cases (Gill, 1980; Mandell *et al*., 1981). Ectopic ureters opening into the uterine cervix are rare, comprising less than 1% of cases (Ellerker, 1958). Small upper pole moities can be difficult to identify on IVU. An alternative investigation which is particularly useful in identifying poorly functioning renal tissue is a radioisotope scan using ^{99m}Tc-dimercaptosuccinic acid (DMSA), but high quality tomography (as in our case) may be diagnostic. In cases of ectopic ureter a careful search for bilaterality is essential if the tragedy of delayed diagnosis is to be avoided.

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Giant Posterior Urethral Calculus

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A case of giant posterior urethral stone is presented and its aetiology discussed. It appears to be the largest stone described in the literature and probably developed in the sacculated posterior urethra behind a urethral stricture which was probably caused by using an external penile incontinence clamp.

Case Report

A 32-year-old male patient was hospitalised because of inability to urinate; he had a urethroperineal fistula through which urine dribbled continuously. Six years previously he had been treated for paraplegia and the only sequela was a neuropathic bladder. To control total incontinence he had been using a penile incontinence clamp.

On examination a hard mass was palpated in the perineum and the skin was macerated with urine and ammonia. A plain film of the abdomen revealed an opaque, ellipsoid mass measuring 72 × 49 mm in the retropubic region (Fig. 1). IVU revealed mild dilatation of the upper tract and marked dilatation of the lower ureters, diminished bladder capacity and a saccular dilatation of the posterior urethra with a huge, radio-opaque density. On retrograde urethrography, saccular dilatation of the posterior urethra was confirmed and no passage was found to the bladder.

In May 1988, under epidural anaesthesia, a perineal urethrolithotomy was performed and a posterior urethral stone measuring 72 × 49 × 52 mm was removed (Fig. 2). The cavity in which the stone was embedded was left open for spontaneous healing. The stricture was incised and a 22 F Foley catheter left in the bladder. The patient was discharged on the 25th post-operative day.

Comment

Urethral stones are often encountered together with urethral strictures or urethral diverticula or both (Marya *et al.*, 1977; Sinha and Rintoul, 1982). Most stones originate in the kidneys (Bridges *et al.*, 1982; Selli *et al.*, 1985) and primary urethral stones are extremely rare.

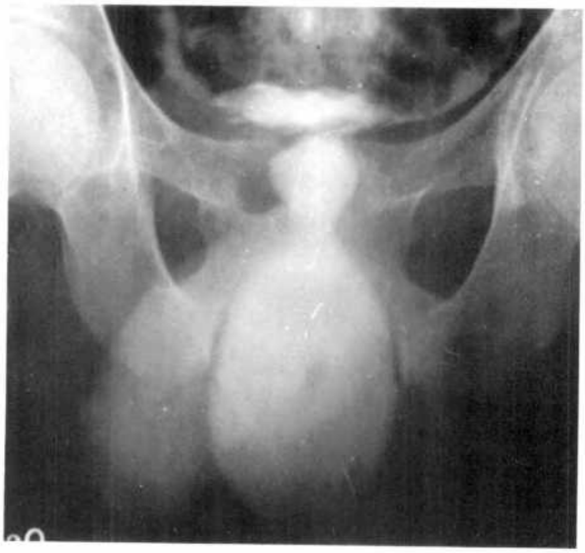

Fig. 1 IVU showing stone and prostatic urethral dilatation.

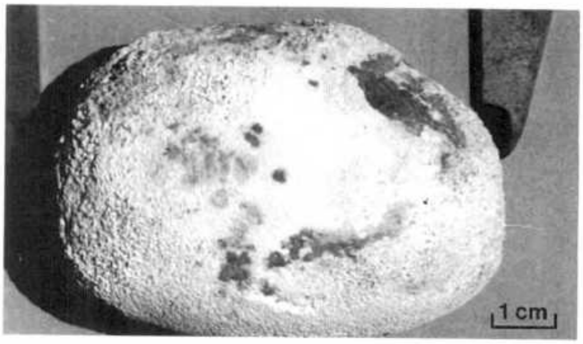

Fig. 2 Stone measuring 72 mm in length.

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Bilateral Malignant Testicular Carcinoid

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Case Report

A 58-year-old, previously fit man developed a painless swelling of the left testis in July 1985. A left inguinal orchiectomy was performed. Histology of the lesion showed a carcinoid tumour (Fig. 1). Post-operatively, his urinary 5-hydroxy-indole-acetic acid (5HIAA) was 77 μmol/24 h (normal < 57 μmol/24 h) but a meta-iodobenzyl guanidine scan for catecholamine-excreting tumour showed no abnormal uptake and at no time was there a clinical carcinoid syndrome.

In January 1987 the patient noticed some thickening in the right testis and his urinary 5HIAA level rose to 433 μmol/24 h. Following a right inguinal orchiectomy the testis was found to contain 3 separate deposits of carcinoid tumour similar in appearance to the left-sided

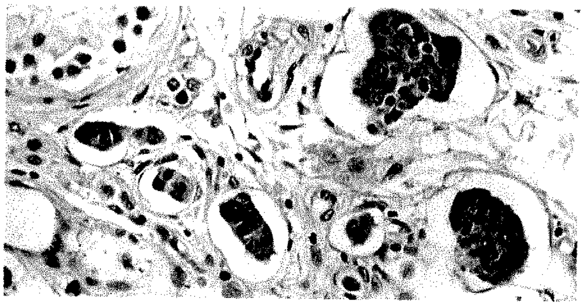

Fig. 1 H and E × 20.

tumour. Computed tomography of the chest and abdomen revealed a 2-cm left para-aortic lymph node at the level of the third lumbar vertebral body but no other abnormality. Eighteen months after the second orchiectomy the patient remains asymptomatic, although the 5HIAA level is elevated at 138 μmol/24 h.

Comment

Little is known about carcinoid tumour of the testis, which was first reported by Simon *et al.* (1954). Talerman and Roth (1986) found only 30 reported cases in a comprehensive review, of which 5 had originated in a teratoma.

We report a case with bilateral testicular carcinoids arising metachronously and with evidence of metastasis to abdominal lymph nodes. There were no clinical features of the carcinoid syndrome, although 24-h urinary 5HIAA levels were elevated.

The treatment of choice for testicular carcinoid is inguinal orchiectomy (Talerman and Roth, 1986). The 24-h urinary 5HIAA can be used to monitor the disease and elevated levels seen in this case were related to residual disease following orchiectomy (Fig. 2). Continued elevation of 5HIAA level after the second orchiectomy suggests that the abdominal lymph node contains hormone-producing carcinoid deposits, but the indication for treatment of metastatic disease is the presence of associated symptoms.

This is the first reported case of bilateral malignant testicular carcinoid.

Acknowledgements

We thank Mr J. O. Lee, Consultant Surgeon, and Dr H. J. Hughes, Consultant Radiotherapist, for their interest and collaboration.

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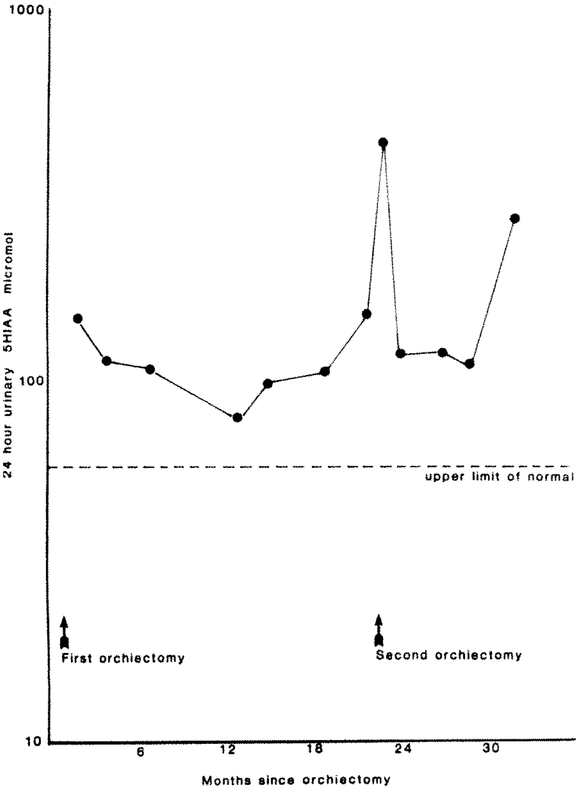

Fig. 2 Levels of 24-h urinary 5HIAA.

Ascites Induced by Interleukin-2 in the Treatment of Renal Cancer

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Interleukin-2 treatment has provided one of the most important recent advances in the management of renal cancer. Fluid retention is reported as a side effect of treatment. This generally manifests as weight gain and pulmonary oedema. We describe the first reported case of ascites related to interleukin-2 therapy occurring in the context of a response to treatment.

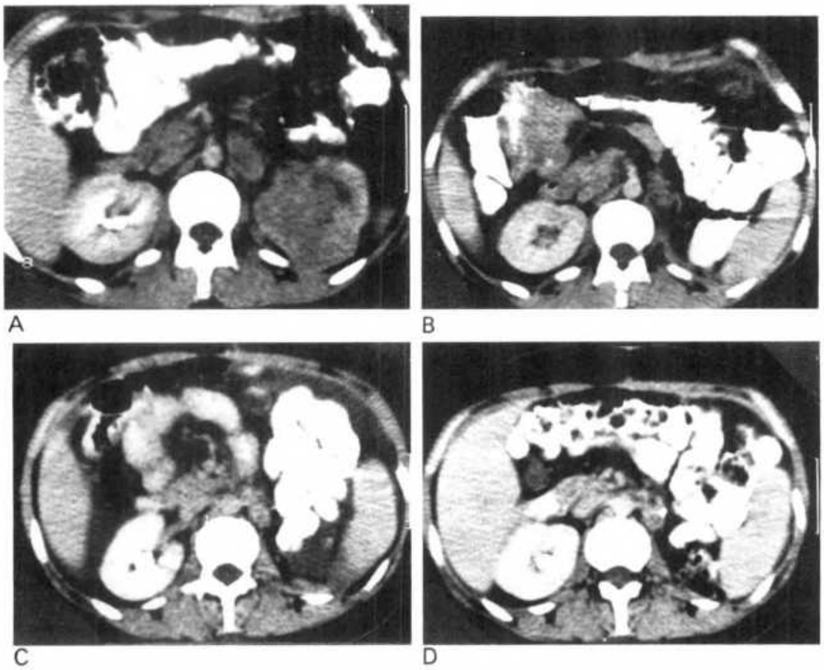

Fig. 1 (A) 8.4.88. Presentation with a right-sided renal tumour and para-aortic lymphadenopathy. (B) 27.5.88. Following nephrectomy. (C) 30.6.88. Ascites and decreased para-aortic lymphadenopathy. (D) 8.9.88. Following treatment.

Case Report

A 19-year-old student nurse presented in April 1988 with frequency, left-sided abdominal pain and intermittent haematuria. An intravenous urogram demonstrated a large mass in the upper pole of the left kidney.

A left nephrectomy and para-aortic lymph node biopsy were performed and showed renal carcinoma metastatic to para-aortic lymph nodes. In view of the presence of metastatic disease, treatment with interleukin-2 was given. This consisted of a continuous infusion of interleukin-2 for 5 days each week for 4 weeks, followed by a 2-week break and then 2 more weeks' treatment. The dosage of interleukin-2 varied between 600 and 1600 μg/day, treatment being titrated against side effects.

During the second week of the first cycle of therapy the patient developed abdominal distension and discomfort. This was unaccompanied by weight gain, congestive cardiac failure, change in serum albumen or renal function. A CT scan performed just after completion of the first month of treatment showed ascites and a 50% reduction in para-aortic lymph node bulk. One week later the patient's abdominal distension had resolved and an abdominal ultrasound scan showed resolution of the ascites. The abdominal distension did not recur with the second cycle of treatment. A further follow-up CT scan performed 2 weeks after the second cycle of treatment showed no recurrence of the ascites and a further reduction in para-aortic lymph node bulk (Fig.). The temporal relationship between interleukin-2 therapy, ascites and the marked clinical response suggests that the ascites was directly caused by interleukin-2 treatment.

Comment

The introduction of interleukin-2 and lymphokine activated killer cell treatment has bought new hope to the management of patients with solid tumours. Significant responses have been reported in up to 60% of patients with renal cancers (Rosenberg *et al.*, 1985). Treatment is associated with fluid retention in 64% of patients treated with interleukin-2 and lymphokine activated killer cells (Rosenberg *et al.*, 1987) and 14% of patients treated with interleukin-2 alone (West *et al.*, 1988). Because of this high response rate, in a previously poorly responding tumour group, it is likely that treatment with this agent will be more widely investigated. This case is reported in order to alert clinicians to the observation that the development of ascites during interleukin-2 therapy does not necessarily represent disease progression. In this case there was clear evidence of objective response associated with transient ascites.

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Urachal Cyst: an Unusual Cause of Hydronephrosis

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The urachus is a patent tract between the urinary bladder and the allantois in early intrauterine life. This degenerates to a fibrous tract between the apex of the bladder and the umbilicus by about the twelfth week of gestation. By adult life, in the majority of individuals, this is closed to nothing more than a fibrous band between the bladder and the umbilicus. An identifiable tract may exist in up to one-third of adults but rarely gives rise to any clinical problem. Cysts of the urachus are well recognised, and they occasionally become infected (Thackray and Symmers, 1978).

We present a patient with a urachal cyst who had an unusual complication.

Case Report

A 60-year-old man with multiple sclerosis presented with a 3-day history of pain and lower abdominal swelling. He did not admit to any upper or lower gastrointestinal symptoms. He had a long history of urinary incontinence. On examination he was apyrexial, haemodynamically stable and well hydrated, with symptoms and signs consistent with the diagnosis of multiple sclerosis. He was almost totally quadriplegic with diminished sensation below T10. Abdominal examination revealed a tense, non-tender 12 × 15 cm mass arising from the pelvis. This was dull to percussion and the mass was thought to be urinary bladder, but catheterisation yielded 1200 ml of clear urine with only partial reduction in the size of the mass.

Haematological and biochemical indices, including liver function tests, were all normal on admission but the ESR was raised at 65 ml in the first hour. Ultrasonography showed a complex mass containing fluid and solid elements (Fig.). The mass appeared distinct from the bladder and was compressing both ureters, with bilateral hydroureter and hydronephrosis more marked on the right side. The radiologists also commented on a hyperechoic lesion 4 cm in diameter high in the right lobe of the liver. Computed tomography confirmed the above findings. At laparotomy a 12-cm mass was found attached to the umbilicus via a fibrovascular cord and intimately related to the postero-superior aspect of the bladder. There were some attached loops of small bowel. The cyst was mobilised, deroofed and drained. It contained 500 ml of purulent-looking fluid. Bacteriological examination of the fluid revealed a *Pseudomonas* contaminant consistent with a chronic low grade infection, but no other pathogens. Histological examination of the cyst wall revealed a thick and fibrous structure with a chronic granulomatous lining. The external surface was lined with peritoneum and the appearances were consistent with those of an infected urachal cyst.

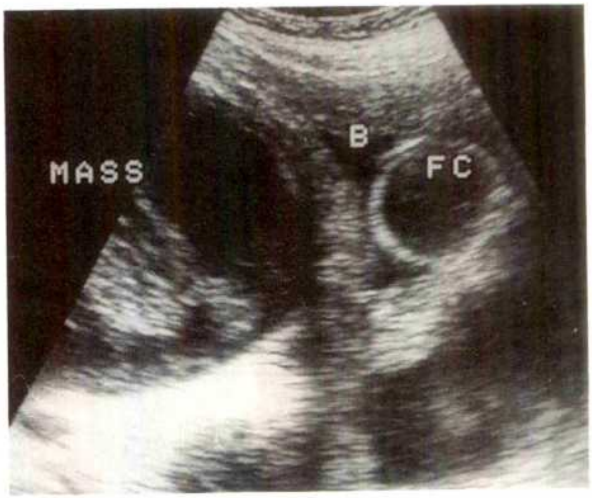

Fig. Mixed density mass intimately related to empty bladder (B) containing a Foley catheter (FC).

The patient made an excellent recovery and was discharged home 10 days after the procedure.

Comment

Obstructive uropathy is one of the many complications of urachal cysts. Chronic infection, peritonitis (Agatstein and Stabile, 1984), carcinomatous change (Shelton *et al.*, 1984) and even prostatism (Standfield and Shearer, 1981) are documented in the literature. Nevertheless, there are no reported cases of direct ureteric compression. In our patient, post-operative ultrasonography revealed complete resolution of the urinary tract dilatation on the left side and incomplete resolution on the right. We believe the residual dilatation may be secondary to this patient's chronic urinary retention.

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Points of Technique

A Simple Method of Urethrovesical Anastomosis in Radical Prostatectomy

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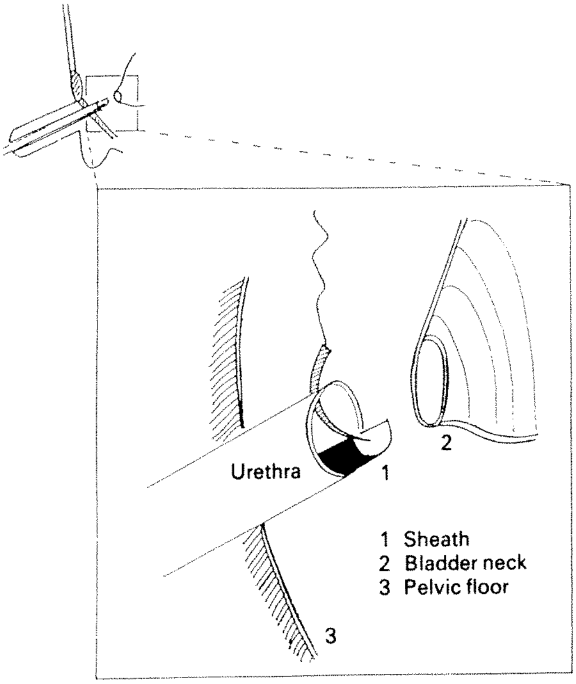
Following the work of Walsh (1986), there has been renewed interest in total radical prostatectomy. At this institute, radical prostatectomy is performed using the Walsh technique.

Placing the sutures correctly at the urethrovesical anastomosis can be difficult. In an attempt to simplify this part of the procedure, we use the half round, supplementary sheath of the Karl Storz optical urethrotome (No. 27068, Storz Catalogue).

The obturated sheath of the optical urethrotome, together with the supplementary sheath, is introduced through the urethra. When visible at the pelvic floor, the obturator and the internal sheath are removed and only the supplementary sheath is left in place. In this way the sutures can be easily placed, since the opposite urethral wall is protected by the metal sheath (Fig.). After inserting the sutures, but before tying them, the sheath is removed and a catheter passed *per urethram* into the bladder. The sutures are then tied.



By using this inexpensive instrument this part of the procedure is simplified and operating time is reduced.

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Increasing Surgical Access to the Retropubic Space

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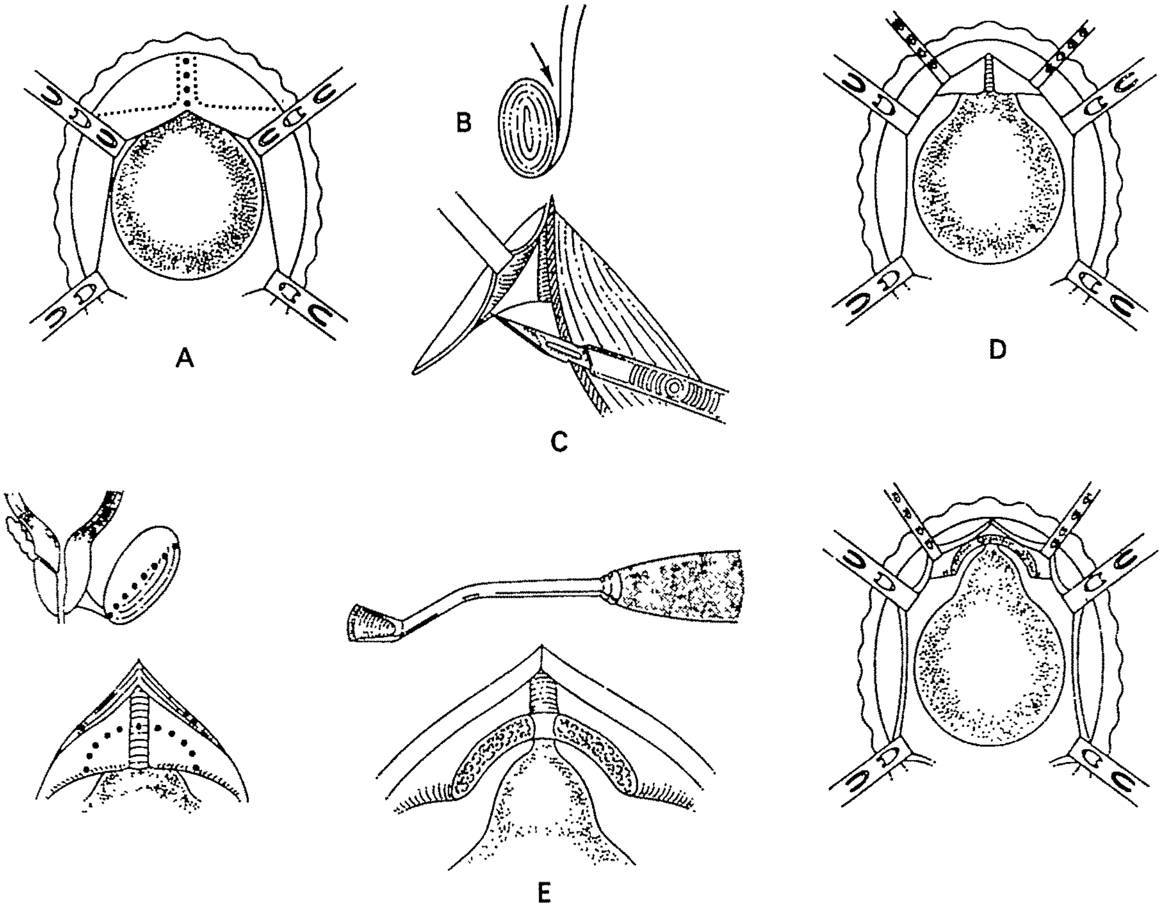
The surgical access to the depths of the retropubic space provided by a midline incision can be greatly improved by the simple procedure of exposing the whole width of the upper margin of the body of the pubis (Fig. 1A).

Because the pubic attachment of the rectus tendons is not to the pubic crest, but spreads widely over the whole of the anterior surface of the pubis down to its inferior margin, it is easily reflected by sharp dissection after a distal prepubic extension of the midline incision (Figs 1B and C). This simple but remarkably effective increase in the lateral exposure (Fig. 1D) is sufficient in itself for most routine retropubic procedures.

Excellent exposure of the sub-prostatic urethra for radical prostatectomy and for the repair of complex pelvic fracture urethral injuries can be achieved without a total prostatectomy, simply by removing the back of the pubis with a Capener's gouge (Fig. 1E) (Turner Warwick, 1972, 1983). This simple procedure takes less than a minute, does not complicate closure and is remarkably bloodless—indeed the increased access greatly



facilitates the control of bleeding from the venous plexus of the anterior pelvic floor.

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Turner Warwick, R. (1973). The management of traumatic strictures and injuries. *Br. J. Surg.*, **60**, 775–781.

Turner Warwick, R. (1983). Urethral stricture surgery. In *Urologic Surgery*, ed. Glenn, J. G. Pp. 689–719. Philadelphia: Lippincott.

Requests for reprints to: R. Turner Warwick, 61 Harley House, Marylebone Road, London NW1 5HL.

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Notices

British Association of Urological Surgeons

President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Annual Meeting: Scarborough. 10–13 July 1990

All correspondence to: M. G. Royle, FRCS, Honorary Secretary, British Association of Urological Surgeons, Royal College of Surgeons, Lincoln's Inn Fields, London WC2A 3PN.

International Continence Society: 20th Annual Meeting

Aarhus, Denmark. 12–15 September 1990

Further information from: Dr J. P. Nørgaard, Institute of Clinical Experimental Research, University of Aarhus, DK-8000 Aarhus C, Denmark.

Simpla Research Prize

The Simpla Research Prize was inaugurated in 1988 and consists of an annual prize of £1000.00 to support a clinical research project. Applicants should submit an abstract of not more than 500 words detailing the way in which, if successful, they would use the prize. These submissions should be made to the Honorary Secretary by 1 April. Entries will be judged by three members of Council nominated at the February meeting and the winner will be announced at the Annual General Meeting.

Dantec Urology Prize

An annual prize is awarded by Dantec for the best scientific paper contributing towards the understanding of the function of the urinary tract, which has been accepted by a medical journal for publication in the United Kingdom. Special consideration will be given to papers relevant to clinical human urology. The prize will be known as The Dantec Award for Contribution to the Understanding of Urinary Tract Function. The prize will consist of a £400.00 travel voucher together with a token presentation gift. The prize will be presented at the BAUS Annual Meeting.

The competition is open only to graduates of British or Irish universities resident in the British Isles. Papers which have been published from 1 January to 31 December of the year preceding the award will be considered. Three members of BAUS Council will be nominated at the February meeting of Council to act as adjudicators. All entries, which must include a reprint of the paper in question, must be submitted by 1 April in the year of entry to the Honorary Secretary of the British Association of Urological Surgeons. The winner of the prize will be announced at the Annual Meeting, when the official presentation will be made.

Shackman Travelling Fellowship 1991

Applications are invited from Medical Practitioners registered in the United Kingdom who are Senior Registrars in an accredited training programme in urology or Consultant Urological Surgeons of no more than 5 years' duration. Applicants of equivalent university status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to urology or to renal transplantation and may be either a laboratory or a clinical investigation.

The closing date for applications is 1 September 1990.

Further particulars from and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB8 9AG.

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Diary

1990

March 28–30	**Association of Surgeons of Great Britain and Ireland. Annual Meeting. Cardiff. Closing dates for abstracts 7th October 1989. Contact Ms Caroline Ross at the Royal College of Surgeons, Lincolns Inn Fields, London WC1. Tel: 01 405 3474**
April 22–26	18th Biennial Congress of the Urological Association of South Africa. Durban, South Africa. Contact Uro 1990, P.O. Box 17008, Durban 4013, South Africa.
April 27–28	Interactive Obstructive Uropathy. Manchester. Contact Mrs G. Trimble, Department of Urology, Withington Hospital, West Didsbury, Manchester M20 8LR
May 5–6	Athenian Days of Urology 1990. Athens, Greece. Contact Professor C. Dimopoulos, Department of Urology, Laiko Hospital, 115 27 Athens, Greece.
May 13–17	**Annual Meeting of the American Urological Association, New Orleans. Contact The Secretary, AUA, 1120 N Charles Street, Baltimore, Maryland 21201, USA.**
May 27–June 3	Urological Society of Australasia. 43rd Annual Scientific Meeting Darwin–Kakadu. Contact ASM Secretariat, Urological Society of Australasia, 145 MacQuarie St, Sydney 2000, Australia. Tel: 27 4461
June 9–10	Société Belge d'Urologie: 55th Congress. Brussels, Belgium. The topic will be "Medical Films on Urology". Contact Dr F. F. Wart, C.H.U-I.M.C.A.G., Division of Urology, Boulevard Zoe Drion 1, B-6000 Charleroi, Belgium.
June 12	First Annual Meeting of the European Society of Paediatric Urology. Amsterdam, The Netherlands. The topic will be Posterior Urethral Valves. Contact Dr P. Mouriquand, "Le Dizenier", 11 impasse Mouillard, 69009 Lyon, France.
June 13–16	Ninth Congress of the European Association of Urology. Amsterdam. Contact QLT Convention Services, Keizersgracht 792, 1017 AC Amsterdam, The Netherlands. Tel: 010 31 20261372
June 24–28	Canadian Urological Association Meeting, Vancouver, British Columbia, Canada. (To be held jointly with members of BAUS). Contact Dr J. P. Collins, Ottawa Civic Hospital, 1053 Carling Avenue, Ottawa, Ontario K1Y 4E9, Canada.
July 10–13	BAUS Annual Meeting, Spa Conference Centre, Scarborough. Contact Secretariat, Royal College of Surgeons, Lincolns Inn Fields, London WC1. Tel: 01 405 1390
September 9–11	Biannual Conference of International Society for Dynamics of the Upper Urinary Tract. Stockholm, Sweden. Contact Anne-Charlotte Kinn, Department of Urology, St Görans Sjukhus, 112 81 Stockholm, Sweden.

Courses which are recommended for Senior Registrar Education are marked with (SR).

All 'BAUS–associated' meetings/courses are printed in bold.

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Book Reviews

Urinary Tract Infection in Clinical and Laboratory Practice.

By Rosalind Maskell. Pp. xi + 268. London: Edward Arnold. 1988. Price £25.00.

This book gives comprehensive coverage of the subject of urinary tract infection in all fields of medicine, *i.e.* paediatrics, general practice, urology, etc. It also brings us up to date on, for example, the different mechanisms whereby one *E. coli* attacks the kidney and another the bladder, on the ubiquity of *Chlamydia* and the laboratory techniques necessary to identify this organism, etc.

The author's clinical management of urological patients cannot be faulted, although it must be confessed that no significant strides have been made in understanding and effectively treating chronic prostatitis. This reviewer would prefer that she abandon the term "neuropathic bladder" (does this word include unstable bladder, and does it differentiate from detrusor failure?), since the term is seldom used in urological literature.

There is good advice on the value of bacteriuria from ileal conduits and in asymptomatic patients. Specific antibiotic regimes are recommended and this suggests that fairly frequent editions will be necessary. The author will thus be able to add recent advances to this most interesting book and make it possible for the urologist to recommend it to both student and practitioner of the specialty for years to come.

Plastic Surgery in the Sexually Handicapped.

Edited by W. Eicher, F. Kubli and V. Herms. Pp. xii + 171. Berlin, Heidelberg, New York, London, Paris, Tokyo: Springer-Verlag. 1989. Price DM178,–.

This book is the Proceedings of an International Satellite Symposium of the 8th World Congress for Sexology. The title of the Symposium was "Reconstructive Surgery in the Sexually Handicapped". The topics covered are Surgical Correction of Breast Deformities, Breast Reconstruction after Mastectomy, Surgical Procedures to help with Genital Malformations, *e.g.* Hypospadias, Epispadias, Congenital and Acquired Penile Deviations. There is also a section on Vaginal Creation and Repair in Women and several contributions describing Gender Reassignment Surgery, both male to female and female to male. Part 6 deals with Penile Prostheses for Impotence and finally there is a section on Vascular Impotence.

Surgery for the sexually handicapped is a subspecialty within Urology and Gynaecology and if good results are to be obtained, these patients should be referred to doctors who have a special interest in the problem. One thing that clearly emerges from this book is that there are a number of techniques to deal with the special situations, but these are not readily found in general textbooks. This book will therefore be of value in larger urological departments where this type of surgery can be undertaken.

Controversies in Urology.

Edited by C. E. Carlton, Jr. Pp. xx + 358. Chicago, London, Boca Raton: Year Book Medical Publishers. 1989. Price £43.00.

This book is a collection of essays by mainly North American contributors (80 out of a total of 86). The editorial policy of an introduction and summary, sandwiching two or more opinions, was hopeful but not always effective. Different views are not necessarily compared and the synthesis not always clear. Much of the presentation of material is rather typically discursive. It has been a matter of editorial policy that contributors of stature should adopt a "thumb in lapel" approach and expound *ex cathedra* without necessarily using references. Surely even the great and good should take account of the opinions of others lest their statements lack academic authority. A compromise approach of a list of references for suggested further reading at the end of a section is equally unsatisfactory.

Many of the problems will be of rather distant practical interest to British urologists. The complex plans for investigation of recurrent stone formers are interesting but inconceivable beyond the metabolic unit with time and facilities to spare. Similarly, the detailed investigation of impotence arguably has little therapeutic consequence. The treatment here is also a little out of date. Much attention has been paid to NPT studies but rather little discussion of papaverine and its side effects. I doubt that many British urologists would wish to give 60 mg in 20 ml of saline as a sighting shot! Some of the discussion hardly relates to burning issues. Few urologists here are likely to consider an inflatable artificial sphincter in exstrophy or to agonise over microsurgical vasovasostomy. The treatment of urethral diverticulum has always seemed rather uncontroversial. The North American approach to issues in urological cancer is predictable but well discussed. The arguments for radical treatment of early prostate cancer, nephrectomy in metastatic renal carcinoma and radical groin dissection in carcinoma of the penis are rehearsed. It is interesting that the field of controversy of node dissection has shifted to proven retroperitoneal disease rather than Stage 1 teratoma. This could even represent the influence of hitherto neglected work of British oncologists!

The discussion of female urology is at time excessively wordy, though helpful. It is amusing to have Stamey put the record straight on the historical development of endoscopic bladder neck suspension.

The selection of issues in paediatric urology is well discussed, notably in relation to urethral valves. I doubt that surgeons in Britain will be persuaded by the mainly psychological arguments to operate on hypospadias before the age of 2 years.

This book is a good read and the cost not exorbitant. The discussion of controversial issues would be more valuable if it were truly transatlantic.

Renal Pathology with Clinical and Functional Correlations. Volumes I and II. Edited by C. C. Tisher and B. M. Brenner. Pp. xxi+942 (Volume I); 925–1598 (Volume II). Philadelphia, London, Mexico City, New York, St Louis, Sao Paulo, Sydney: Lippincott. 1989. Price £120.00.

In the preface to these excellent volumes, Professors Tisher and Brenner stress the enormous benefit to the specialty of nephrology derived from the happy "marriage" between nephrologist and nephropathologist. The majority of the chapters are successfully co-authored by both a pathologist and a physician. The book is divided into 7 major sections—General Considerations, Glomerular Diseases, Tubular and Interstitial Diseases, Vascular Diseases, Heredofamilial Disease, Neoplasms and Transplantation—with a total of 51 chapters and 101 expert and predominantly American contributors.

The chapters are well written with a uniformity of style and format indicating tight editorial control. Each chapter includes in-depth discussion of the pathology, pathogenesis, clinical features, prognosis and treatment of the disease in question, in addition to an extensive and up-to-date bibliography containing many 1986 and 1987 references and some from 1988.

Chapters on AIDS and drug addiction nephropathies and cyclosporin nephropathy are especially welcome. The illustrations are generous in number and, in general, photomicrographs are of good quality. The index is duplicated in each volume and is intelligently devised.

The reviewer cannot praise this book too highly and recommends its purchase to all pathologists who handle renal material on a regular basis. Although the section on transplantation is excellent, there is insufficient coverage of neoplasms to justify its purchase by the urologist or urological pathologist. At £120 this book represents excellent value and it will probably become an essential addition to nephrologists' and hospital libraries.

Clinical Practice in Sexually Transmissible Diseases. Second edition. By D. H. H. Robertson, A. McMillan and H. Young. Pp. 520. Edinburgh, London, Melbourne, New York: Churchill Livingstone. 1989. Price £49.50.

In 1981, 1 year after the first edition of this book was published, the epidemic of the acquired immune deficiency syndrome, AIDS, began. The second edition of the book gives a full account of HIV infections and the other persistent virus disorders that can be transmitted sexually. The first edition devoted 50 pages to virus infections; the second devotes 120, yet is only 50 pages longer overall. The classical sexually transmissible diseases, such as syphilis and gonorrhoea, however, are by no means neglected and much new and important information about them has been included.

Much of the information in this book is relevant to urological practice and it should be available to all urological surgeons as a reference volume.

Ultrasound of the Prostate. By B. D. Fornage. Pp. xii+333. Chichester, New York, Brisbane, Toronto, Singapore: John Wiley. 1988. Price £95.00.

The reviewer remembers meeting the author 10 years ago and being enormously impressed by his command of English. Neither his talents nor enthusiasm stopped there. He had become interested in, among other things, "Ultrasound of the prostate gland". This book represents the result of more than a decade of work on this subject by a dedicated individual. All of the text and a large proportion of the many images are attributable to Dr Fornage, the whole being at the same time an exhaustive review and a personal experience. There is an excellent bibliography to 1987. The approach is thorough and methodical, starting with clearly illustrated sections on gross anatomy, instrumentation and examination techniques, normal ultrasonic anatomy, artefacts and pitfalls. There follows an in-depth discussion of ultrasound appearances in benign and malignant diseases and their effects on the upper urinary tract. Intra-operative, post-operative and post-therapy features are considered. There is a detailed chapter on ultrasound guided biopsy followed by a valuable discussion of transrectal voiding cystourethrosonography. The concluding chapters compare the utility of different ultrasound techniques, the relation to other imaging modalities and the future of ultrasound as seen through the eyes of both the clinician and the radiologist.

The strength of this book lies in the number and quantity of the images and illustrations supported by a concise, readable text which skilfully presents an in-depth, critical, up-to-date review of the world literature supported by a wealth of personal experience. The author is honest enough to admit that the heterogeneous nature of appearances in the abnormal prostate are such that it is not always possible to differentiate reliably between benign and malignant disease with ultrasound alone and that its present role is most successful in assisting guided biopsy of suspicious lesions, improving local staging, assessing effects on the urinary tract and monitoring local response to treatment. The place of ultrasound in screening for prostate cancer is also sensibly criticised. Any urological department contemplating the introduction of ultrasound for the assessment of prostate disease would be well advised to purchase, inwardly digest and then regularly refer to this excellent book.

BRITISH JOURNAL OF UROLOGY

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Morris, J. A., Oates, K. and Staff, W. G. (1986). Scanning electron microscopy of adenomatoid tumours. *Br. J. Urol.*, **58**, 183–187.

References to books should be as follows:

Wright, F. S. and Howards, S. S. (1981). Obstructive injury. In *The Kidney*, ed. Bremner, B M. and Rector, F. C. Second edition. Volume II Chapter 38, pp. 2009–2044. Philadelphia: Saunders.

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REVIEW

Alternatives to Prostatectomy

J. McLOUGHLIN and GORDON WILLIAMS

Department of Surgery, Royal Postgraduate Medical School, Hammersmith Hospital, London

Benign prostatic hyperplasia (BPH) is found in 70% of men in their seventies and up to 90% of men in their eighties. It is the most common growth in man. In 1985 over 34,000 prostatectomies were performed in the United Kingdom. It has been estimated that the probability of a 40-year-old man undergoing a prostatectomy during his lifetime is 29% (Glynn *et al.*, 1985). Approximately 90% of patients undergoing prostatectomy will have a transurethral resection (TURP) (Mebust, 1988). The mortality rate from TURP has declined steadily over the last 3 decades, with rates as low as 0.2% quoted in recent surveys (Mebust, 1988), and it is now considered to be the optimal treatment for patients with prostatic outflow obstruction (Chisholm, 1989). However the results of prostatectomy are not perfect. It has a significant morbidity rate and some patients remain symptomatic (Malone *et al.*, 1988). In addition, an appreciable number require a second prostatectomy after a relatively short follow-up period (Roos and Ramsey, 1987). Malone *et al.* (1988) also observed that patients undergoing TURP for acute retention had 3 times the expected death rate in the first year after operation.

The 2 main dilemmas facing the urologist are the variability in the course of patients with untreated prostatic symptoms and whether the pre-interventional diagnosis of bladder outflow obstruction improves the symptomatic response to treatment. Both Craigen (1969) and Castro *et al.* (1971) observed that patients' symptoms fluctuated widely with time, whilst Ball *et al.* (1981) and George *et al.* (1986) found that patients awaiting elective surgery did not necessarily deteriorate with time. This makes it difficult to interpret short-term clinical trials of new treatments because any improvement that occurs may be spontaneous. Prognostic indicators for a patient who presents to the urologist with the symptom complex of "prostatism" are difficult to identify. Symptoms themselves are an unreliable index of obstruction, with the exception of increased hesitancy when attempting to void with a full bladder (George *et al.*, 1986) and their severity in an individual patient does not predict the likelihood of retention or progression with time. There have been variable reports on the effectiveness of urodynamic measurements in identifying outflow obstruction or predicting which patients will benefit from TURP (Graversen *et al.*, 1989).

Most patients attend the urologist for symptoms and it is by the amelioration of these symptoms that a patient gauges the success of his treatment. Kadow *et al.* (1988) observed that 71% of patients obtained symptomatic relief following TURP compared with 56% after conservative treatment (bladder drill plus either Pro-Banthine or phenoxybenzamine), despite objective evidence of improvement occurring only in those who had undergone prostatectomy. The role of surgery in patients who are symptomatic, but without evidence of detrusor decompensation or embarrassment of their upper urinary tract, should be considered against that of a more conservative approach to management which may also result in symptomatic relief.

Mechanism of Obstruction

The mechanism by which the prostate restricts bladder outflow is thought to be partly due to a mechanical "static" effect caused by the bulk of the prostatic mass and partly to a "dynamic" muscular component resulting from stimulation of adrenergic alpha receptors in the prostatic fibromuscular stroma, capsule and bladder neck. The relative importance of these factors has been disputed.

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Brooks *et al.* (1983) felt that the prostatic bulk was the main component, but Furuya *et al.* (1982) postulated that muscular tone accounted for 40% of the total outflow obstruction. It may be that the most effective treatment should be aimed at reducing both obstructive components and that a treatment reducing either one or the other will have only a limited effect.

Reduction of the Dynamic Component of Obstruction

Alpha blockade has been the mainstay of treatment aimed at reducing muscular tone. The first alpha blocker used was phenoxybenzamine which non-selectively blocked both alpha-1 and alpha-2 receptors with a high incidence of side effects (Caine, 1986) consequent on the loss of alpha-2 receptor mediated regulation of noradrenaline. Prazosin (Kirby *et al.*, 1987), Terazosin (Dunzendorfer, 1988), and Indoramin (Iacovou and Dunn, 1987) are recent additions and exert selective alpha-1 blockade with fewer side effects. Approximately 70% of patients receiving alpha blockers can be expected to obtain symptomatic relief (Caine, 1986). In outflow obstruction the normal detrusor response to sympathetic stimulation changes from predominantly beta to alpha, a change correlated with bladder instability. Many of the studies using alpha blockade have shown that the degree of symptomatic improvement from associated detrusor instability occurs faster than would be expected from the removal of the outflow obstruction by surgery or even in the absence of objective evidence of relief of obstruction (Ramsey *et al.*, 1985). Alpha blockade may thus produce a direct effect on the detrusor to produce symptomatic improvement even in the absence of relief of obstruction. Kadow *et al.* (1988) observed that to a large degree the relief of instability associated with obstruction was how the patient gauged the success of his treatment, so it is not unexpected that alpha blockade will produce such a high symptomatic response rate. The reduction in outflow resistance has been less consistent, with some studies (Chapple *et al.*, 1989) revealing a clear reduction as demonstrated by an improved flow rate associated with a reduction in voiding pressure, whilst others (Dunzendorfer, 1988) left patients with a flow rate on treatment low enough to suggest a high probability of residual obstruction. With the exception of the study by Dunzendorfer (1988), none of the trials evaluating alpha blockade has been over 3 months in duration. This leaves open the question of what becomes of patients on long-term therapy with respect to continued response to treatment, patient compliance and incidence of progression of disease. Until this information is available, alpha blockers can be safely recommended only to patients who have been fully evaluated by a urologist and are awaiting definitive treatment.

Reduction of the Static Component of Obstruction

Testosterone is necessary for the development and maintenance of the prostate. In addition, oestrogens, which increase the number of androgen receptors, may enhance the development of BPH (Chisholm, 1989). Therapies which alter the endocrine environment are primarily aimed at reducing the bulk of the prostate by producing involution of the glandular component and thereby reducing the static component of the obstruction. Hormonal therapy may also exert an effect by facilitating the beta-adrenergic response of the urethra (Raz *et al.*, 1973) or by reducing urethral prostaglandin concentrations rather than affecting the gland itself (Matos-Ferreira *et al.*, 1987). Hormonal therapy (including LHRH analogues, androgens, oestrogens and antiandrogens, alone or in combination) has, on the whole, been disappointing, with side effects such as loss of libido and the development of erectile dysfunction limiting the potential for wider usage. A number of trials have reported a decrease in prostatic size and an increase in flow rate but small patient numbers and short-term follow-up have limited the impact of many of these studies. The effect of placebo on the results of drug trials with respect to symptomatic improvement may be appreciable (Castro *et al.*, 1971) and has also to be taken into account, since a number of studies did not employ a placebo control.

More recently, 5 alpha reductase inhibitors which block the enzyme responsible for the conversion of testosterone to the more active dihydrotestosterone have been described. These suppress prostatic levels of dihydrotestosterone by up to 92% within a week (Wilson *et al.*, 1989), with a resultant decrease in prostatic volume of 28% within 6 months, without altering systemic levels of testosterone. They appear to produce none of the side effects usually associated with hormonal therapy (McConnell *et al.*, 1989). Trials evaluating 5 alpha reductase inhibitors are still at a very early stage.

The role of hyperthermia in the management of BPH has recently been investigated. The principle is once again to reduce the static component of obstruction by reducing prostatic size. Servadio *et* *al.* (1989) observed that 49% of patients catheterised for urinary retention voided spontaneously following treatment, whilst Lindner *et al.* (1987) described relief of retention in 5 of 6 patients. Initial results were good, with few side effects and the prospect of these patients being treatable on an out-patient basis. Longer-term randomised controlled studies are still awaited to clarify the duration of response to this form of treatment and also the development of complications.

Mechanical Reduction of Outflow Resistance

The concept of prostatic dilatation is not new. Early attempts to dilate the prostatic urethra were by the use of metal dilators (Mercier, 1850) or by the introduction of the surgeon's index finger at the time of cystotomy (Hollingsworth, 1910). These studies based their success on symptomatic criteria and lacked objective assessment of results or follow-up. This was also true of later studies by Deisting (1956), who used a modification of Mercier's metal dilator and claimed excellent results over a prolonged period. Castaneda *et al.* (1987) and Reddy *et al.* (1988) used a balloon to dilate the prostate. This was inserted transurethrally and expanded in the prostatic urethra to a diameter of 25 mm. They recorded both symptomatic and flow rate improvements, but numbers of patients and follow-up were limited. To date, the largest study in which patients were assessed both cystometrically and symptomatically before and after dilatation is by Gill *et al.* (1989). Their series comprised 48 symptomatic patients with bladder outflow obstruction demonstrated on cystometry and 19 patients with urinary retention who were dilated with 20 and 25 mm balloons on an out-patient basis. The results were disappointing, with only 11% of patients in the obstructed group rendered unobstructed and only 3 in the retention group voiding spontaneously following the procedure. The results of dilatation using larger balloons are still awaited but appear only slightly more encouraging (McLoughlin *et al.*, unpublished data). The mechanism of action has been postulated to be splitting of the prostatic commissures and exhaustion of the elasticity of the prostate (Castenada, 1987), but Gill *et al.* (1989) found that commissural splitting was not associated with successful dilatation. A common feature of balloon dilatation in all studies has been the low incidence of complications and very low mortality.

The principle of placing an artificial, inert prosthesis into the prostatic urethra to reduce outflow resistance has recently become the subject of considerable interest. Fabian (1980) first described the use of a "urological spiral" placed cystoscopically into the prostatic urethra in 2 patients, producing relief of retention. The advantage of this device was that it had a "tail" by which it could be grasped; this allowed it to be withdrawn and replaced under local anaesthesia. Fabricius *et al.* (1983) showed that a number of patients treated with these spirals developed complications such as incontinence, urethral strictures, encrustation or displacement, leading to their removal or replacement. A gold plated modification of this device (the "Prostakath") is at present under evaluation (Harrison and de Souza, 1990), but initial results are not promising. The use of self-expanding tubular stainless steel prostatic stents (Medinvent Wallstent) has recently been described (Williams *et al.*, 1989) in patients with retention of urine who are unfit for surgery. These stents are flexible enough to conform to the contours of the prostatic urethra and can be inserted either cystoscopically under direct vision or under fluoroscopic control (Williams *et al.*, 1989) or a combination of cystoscopic and ultrasound control (Chapple *et al.*, 1990). Initial follow-up suggests that they are safe and reliable in selected patients (McLoughlin *et al.*, 1990), but longer follow-up is required before the wider use of these stents can be advocated.

Summary

The danger of the treatments described are that patients may be treated without referral to a urologist. Investigations to determine whether genuine obstruction is the cause of their symptoms may not be performed and follow-up to exclude the side effects of their outflow obstruction or indeed their treatment may not be carried out. In addition, in cases where digital palpation does not alert the clinician to the possibility of prostatic malignancy, the loss of specimens for histological interpretation may lead to missed diagnoses.

In summary, the alternatives to prostatectomy are still limited. Hormonal manipulation, hyperthermia and prostatic dilatation using the smaller balloons have no role at present in symptomatic patients. The role of larger balloons has still to be determined. Alpha blockade, while achieving relief in the short-term, still requires long-term objective follow-up studies in patients with urodynamically proven obstruction to assess patient compliance and the effects of treatment before it can be recommended as a long-term alternative. Similar information is also required before the efficacy of hyperthermia in patients with retention can be determined. For high risk patients with a limited life expectancy who present with retention of urine, prostatic stents may have a role, but once again long-term follow-up data are required before this treatment can be advocated in fitter or symptomatic patients.

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Continent Cutaneous Ileostomy (Kock Pouch) prior to Renal Transplantation

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Summary—Two patients in end-stage renal failure and with neurogenic bladders due to spina bifida complicated by myelomeningocele were considered for renal transplantation.

One patient had had a right nephrectomy and urinary diversion via an ileal conduit; the other, after various external drainage procedures (cystostomy, bilateral nephrostomy), had had a tubular ileocystoplasty. Both underwent 2 surgical procedures prior to renal transplantation: in case 1 we performed a left nephrectomy and then ileal conduit removal + Kock pouch; in case 2 a bilateral nephrectomy was performed via 2 posterior incisions and then we removed the ileocystoplasty and formed the pouch.

The continent ileostomy was formed according to the original technique with slight modifications. The patients have been followed up for 12 and 15 months after transplantation.

Transintestinal urinary diversion was first introduced in association with renal transplantation by Kelly *et al.* (1966). Since then, several cases have been reported in the literature, especially paediatric patients whose lower urinary tract was not suitable for graft ureter reimplantation (Firlit and Merkel, 1977; Krieger *et al.*, 1980; Williams *et al.*, 1980). We describe the use of a continent cutaneous ileostomy in 2 renal transplant patients in end-stage renal failure.

Case Reports

Case 1. T.G., a 34-year-old woman, presented in end-stage renal failure for pre-transplant investigation. She had a neurogenic bladder due to spina bifida and myelomeningocele with bilateral reflux, recurrent urinary infections and chronic pyelonephritis. She had undergone the following surgical procedures: amputation of the right leg for osteomyelitis in 1977, left nephrectomy for pyonephrosis in 1981 and external urinary diversion via an ileal conduit in 1981. Her renal function continued to deteriorate and she began chronic haemodialysis in April 1984.

Pre-transplant evaluation consisted of standard investigations with particular attention being paid to the lower urinary tract. Cystoscopy showed a low capacity bladder with no sphincteric mechanism and total incontinence.

Supravesical urinary diversion was mandatory in view of renal transplantation. Pre-transplant immunological preparation consisted of 3 whole blood transfusions without immunisation of the patient.

Right nephrectomy, removal of the ileal conduit and formation of a Kock pouch had been carried out through a midline incision in June 1987.

The pouch was formed as described by Kock *et al.* (1982) and later modified by Skinner *et al.* (1984) with the following modifications:

1. The afferent limb crossed the abdominal cavity (Fig. 1) to be placed in contact with the iliac vessels (secondarily receiving the kidney graft), through a peritoneal window.
2. A small pig-tail catheter was left in the afferent limb (Fig. 1) to facilitate limb identification and dissection during renal transplantation. It also allowed continuous irrigation of the pouch in the anuric pre-transplant period, to facilitate mucus evacuation and pouch distension.

A cutaneous stoma was placed in the right iliac fossa and transplantation planned for the opposite side. A cadaver kidney became available in August 1987, when the patient had completely recovered from the first operation and the pouch had reached a capacity of 400 ml. The graft was placed in the left iliac fossa through a j-shaped conventional incision; vascular anastomoses

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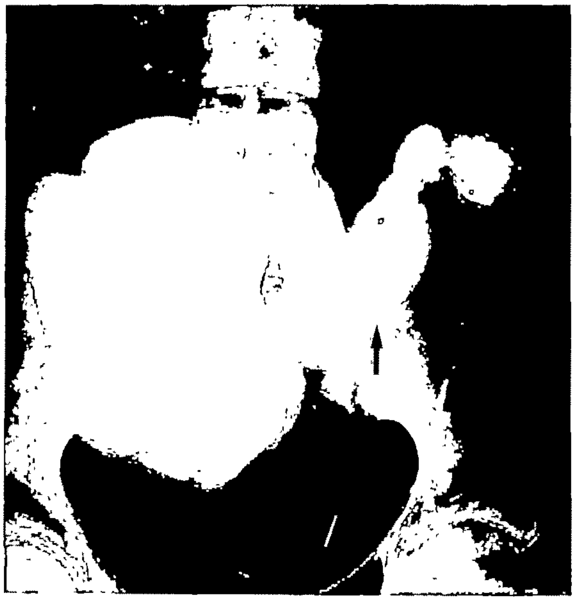

Fig. 1 The afferent limb of the pouch (↑) crosses the abdominal cavity from left to right; the pig-tail catheter (↑↑) is placed in the afferent limb.

were performed as usual; the afferent limb was dissected following the pig-tail catheter and a direct uretero-ileal anastomosis was performed. The early post-operative period was marked by immediate diuresis (total ischaemia time of 22 h) and there were no complications.

The patient was discharged 1 month post-operatively with normal renal function, normal IVU and retrograde pouch contrastography showing absence of reflux, good pouch capacity and complete evacuation. The patient was able to self-catheterise with a standard Foley catheter.

The following findings were noted 15 months after transplantation (Fig. 2). The patient catheterised 3 to 4 times per day with a nocturnal interval of 7 h; the pouch capacity exceeded 700 ml; a little mucus was still present. Only transient bacteriuria was observed with no evidence of urinary infection. Serum creatinine was 89 μmol/l.

Case 2. S.G., a 34-year-old white male, was referred for renal transplantation. He was born with a neurogenic bladder due to spina bifida and myelomeningocele and later developed bilateral hydronephrosis and deterioration of renal function. He underwent surgical cystostomy, bilateral surgical nephrostomy and tubular ileocystoplasty with reimplantation of the ureters in the ileal graft.

His renal function continued to deteriorate and in 1973 he started chronic haemodialysis. His condition improved and his subsequent marriage produced 2 children.

On examination his bladder was found to be unsuitable for ureteric reimplantation and there was infected reflux in both kidneys (Fig. 3). Supravesical urinary diversion was considered mandatory before transplantation.

Immunological preparation consisted of 3 whole blood transfusions with formation of cytotoxic antibodies to 37% of HLA antigenic panel. He underwent bilateral nephrectomy in September 1987 through 2 posterior incisions; 15 days later, through a midline incision, the previous ileocystoplasty was removed and a Kock pouch was formed.

A cadaver kidney became available in December 1987 and was placed in the left iliac fossa via a J-shaped conventional incision. The renal vessels were anastomosed end-to-side to external iliac vessels and the ureter was sutured directly to the afferent limb of the pouch.

The early post-operative period was marked by prolonged anuria due to acute tubular necrosis (total ischaemia time 20 h). Haemodialysis was necessary twice in the first 2 weeks but after day 20 the patient had a normal diuresis and his serum creatinine fell to normal levels. There were no other complications and he was discharged 50 days after transplantation with normal renal function, normal IVU and no evidence of reflux from the pouch to the graft. He was able to self-catheterise and to perform periodic pouch irrigation for evacuation of mucus.

Twelve months after transplantation, these findings were confirmed (Fig. 4). The patient self-catheterised 3 to 4 times per day with a pouch capacity of 900 ml and a nocturnal interval of 8 h. Serum creatinine was 110 μmol/l and periodic bacteriuria was observed without evidence of urinary infection.

In both cases a triple drug immunosuppresive regimen was used, including prednisone, azathioprine and cyclosporin (Table).

Discussion

Major abnormalities of the lower urinary tract often lead to chronic renal failure, usually from chronic infection and pyelonephritis. Most of these patients undergo several surgical procedures to reconstruct the lower urinary tract or to divert urine, and renal transplantation has been considered a high risk procedure. Since the first observation by Kelly *et al.* (1966), several cases have been reported by Glass *et al.* (1985) and Beurton *et al.* (1986). We have performed 9 ileal conduit procedures in 6 patients undergoing renal transplantation.

Pre-transplant assessment should be much more detailed than usual, in these cases particularly if they have already undergone urinary diversion. Culture of the bladder or intestinal conduit must be carried out and retrograde opacification of the bladder or conduit is mandatory to investigate morphology and the presence of reflux. Endoscopic and urodynamic investigations are important when the bladder is still in place, even if non-functioning because of supravesical urinary diversion, since in some cases its functions can be restored after transplantation.

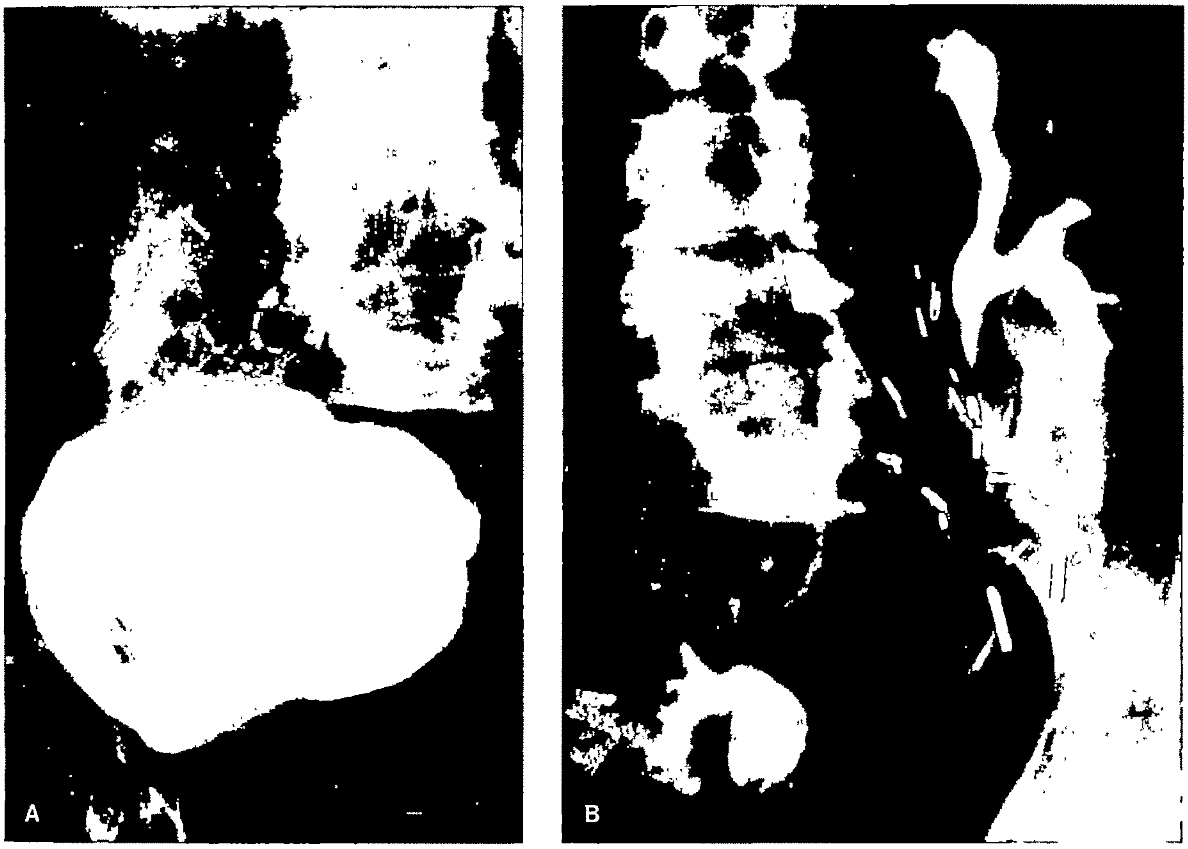

Fig. 2 Case 1. (A) Retrograde pouch contrastography showing good pouch compliance and absence of reflux. (B) Normal IVU.

As in non-transplant patients, a standard transintestinal cutaneous ureterostomy has the disadvantage of continuous urine leakage and the need for an external collecting device.

Improvements in pre-transplant patient preparation and post-transplant immunosuppressive regimens (particularly reduction in steroids) now make it possible to undertake major abdominal surgery which only a few years ago was considered hazardous. Thus we have been able to form a Kock pouch prior to renal transplantation in 2 selected patients.

Our policy is to limit this treatment to highly selected cases. Patient motivation and collaboration are important when performing any kind of continent diversion; they are even more important when associated with renal transplantation, because patients in end-stage renal failure with major abnormalities of the lower urinary tract often require several surgical procedures before transplantation. They should be in good general condition in order to withstand repeated surgery and problems associated with the healing of internal sutures.

Our 2 patients underwent 2 operations prior to transplantation (case 1: excision of the remaining kidney and removal of the ileal conduit + Kock pouch; case 2: bilateral nephrectomy and removal of the ileocystoplasty + Kock pouch). Our modifications to the original technique met their special needs. Both patients were anephric and continuous irrigation was mandatory to ensure mucus evacuation and hydraulic pouch distension. The small pig-tail catheter proved helpful in the dissection of the afferent limb at the time of transplantation. A longer afferent limb was necessary in order to fix the pouch to the internal rectum fascia, and also to have the afferent limb extraperitoneal, close to the iliac vessels where the transplant was scheduled.

There should be little delay between preparation of the Kock pouch and renal transplantation because the anephric state is often complicated by

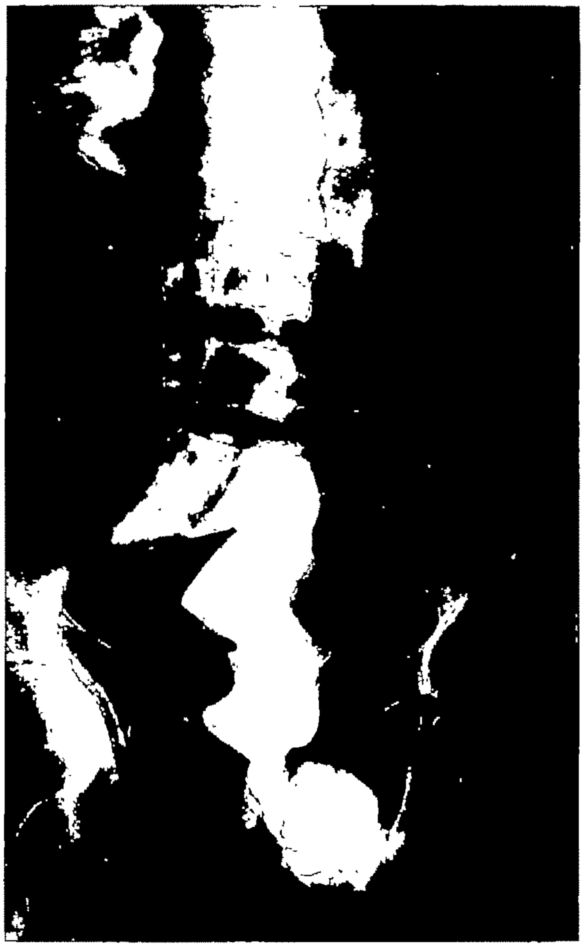

Fig. 3 Case 2. Ileocystoplasty with bilateral complete reflux.

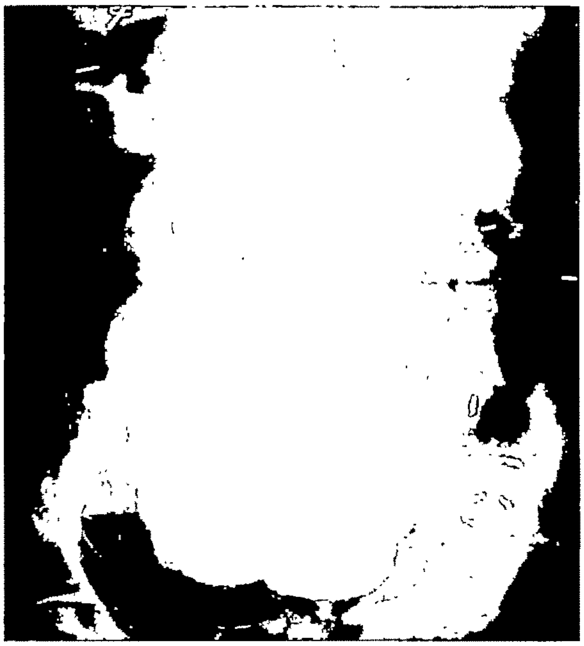

Fig. 4 Case 2. Retrograde opacification showing high pouch compliance and absence of reflux.

Table Immunosuppressive Regime following Transplantation.

	Early post-operative period		*Last out-patient visit**	
	drug regimen	*mg*	*drug regimen*	*mg*
T.G.	Prednisone	20	Prednisone	10
Case 1	Azathioprine	75	Azathioprine	25
	Cyclosporin	400	Cyclosporin	400
S.G.	Prednisone	50	Prednisone	15
Case 2	Azathioprine	75	Azathioprine	100
	Cyclosporin	400	Cyclosporin	420

* Case 1 = 15 months; Case 2 = 12 months.

severe anaemia and fluid retention. In addition, continuous pouch irrigation causes discomfort to the patient when too prolonged.

To reduce waiting time, recipients with a complex urinary diversion should have a common blood group and no cytotoxic antibodies in order to increase the possibility of finding a cadaver donor. If a living related donor is available, transplantation can be scheduled in advance.

Both of our recipients were blood group A but one had almost 40% cytotoxic antibodies. The large number of group A donors allowed us to find a suitable kidney within 6 weeks.

Major abnormalities of the lower urinary tract are no longer an absolute contraindication to renal transplantation, but these patients must undergo careful pre-transplant investigations. If they already have urinary diversion, a check should be made for foci of infection and urodynamic investigation of the non-functioning bladder (if still in place) should be done with a view to undiversion at the time of transplantation. Ileal conduit diversion is the procedure most frequently used in transplant patients.

We have shown that in selected cases a continent diversion can be considered. Patient motivation and careful pre-operative investigations are key factors in our efforts to achieve success.

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Ureterocalicostomy for Reconstruction of Complicated Pelviureteric Junction Obstruction

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Summary—Seven patients with complicated pelviureteric junction (PUJ) obstruction underwent reconstruction by means of ureterocalicostomy; 5 had undergone previous surgery and 2 had primary obstruction. Radiographic studies showed resolution or improvement of the obstruction in 5 patients, who remain asymptomatic 15 to 47 months (mean 30) post-operatively. Obstruction persists in 1 patient and the other developed renal artery thrombosis with subsequent loss of the kidney. It was concluded that ureterocalicostomy can provide long-term, successful reconstruction of a complicated PUJ obstruction, but significant complications may be associated with the procedure.

Pyeloplasty is the standard operation for correction of primary PUJ obstruction. However, an alternative form of reconstruction may be required when the renal pelvis is relatively inaccessible, as may occur in patients with an intrarenal pelvis or peripelvic fibrosis. Ureterocalicostomy is an infrequently used procedure which can provide an alternative means of reconstruction for such patients. We have reviewed our recent experience with ureterocalicostomy in an attempt to define indications and results. A review of the techniques used and complications encountered is included to delineate factors which may lead to failure.

Patients and Methods

Since 1982, 7 patients have undergone ureterocalicostomy. The group comprised 6 males and 1 female, ranging in age from 21 to 54 years (mean 41). In 5 patients the PUJ obstruction was related to previous surgery; 3 of these operations had been for stone disease, 1 for primary PUJ obstruction and 1 a renal allotransplantation. Two patients had undergone no previous urological operations. One of them underwent ureterocalicostomy because of a PUJ obstruction associated with an intrarenal pelvis and the other because of extensive fibrotic changes which made dissection of the left renal pelvis impossible. The latter patient (HS) had systemic lupus erythematosus (SLE) and had undergone previous abdominal surgery for biliary obstruction.

In all patients the diagnosis of obstruction was based on a history of flank pain or declining renal function and a combination of antegrade, retrograde and/or intravenous urography. Nuclear renography was also used in 2 cases.

A flank approach was used in 4 patients, including the 2 with primary PUJ obstruction. A transabdominal approach was used for the renal allograft recipient and in 2 other patients where it was felt that bowel interposition might be required. Renal parenchyma was excised from the anastomotic site in 6 of the 7 patients. In 3 patients the renal artery was clamped during the procedure in order to minimise potential blood loss. In all cases the anastomosis was performed over an internal stent and a Penrose or Jackson-Pratt drain was left in place for external drainage. Additional drainage by nephrostomy tube was used in 2 cases. In 2 cases an omental or peritoneal flap was brought to the anastomotic site.

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Results

The results are summarised in the Table. Estimated intra-operative blood losses and peri-operative transfusions are also tabulated.

Follow-up for these patients ranged from 4 to 47 months (mean 23). One patient suffered significant early post-operative complications, including gram-negative septicaemia and a pulmonary embolus. This patient was treated successfully and suffered no long-term sequelae. Long-term success was achieved in 5 patients as defined by relief of symptoms and improved radiographic studies confirming prompt function and drainage (Fig.).

There were 2 failures. One patient (MS) developed renal artery thrombosis and lost the kidney. This insulin-dependent diabetic female had undergone extended pyelolithotomy elsewhere for a staghorn calculus and now had a secondary PUJ obstruction in a poorly functioning kidney. She was 1 of the 3 patients in whom the renal artery was clamped intra-operatively. Significant hypertension was noted in the immediate post-operative period, when a technetium renal scan showed no flow to the kidney. Simple nephrectomy was performed 5 months later. In the other patient (JC), obstruction recurred 4 months post-operatively. This renal allograft recipient had already failed one attempt at operative reconstruction of his ureteric obstruction. Salvage reconstruction was then accomplished with a ureterocalicostomy between the native ureter and an upper pole calix. This is the single patient in whom there was no excision of overlying parenchyma. He is currently managed with an internal stent and maintains excellent renal function 2 years post-operatively.

Discussion

Ureterocalicostomy is an infrequently performed operation. The primary indication is to reconstruct a complicated PUJ obstruction. The procedure was first used successfully in 1932 in a woman with stones in a solitary kidney (Neuwirt, 1947, unpublished observations). Couvelaire *et al.* (1964) reviewed their experience with ureterocalicostomy and reported good results in 4 of 8 patients. They were the first to suggest the importance of resecting overlying parenchyma at the site of the anastomosis. Hawthorne *et al.* (1976) reviewed 50 cases from the literature and found the success rate of ureterocalicostomy to be 72%. Since 1976 there have been isolated case reports and 2 retrospective reviews of the use of ureterocalicostomy in adults (Ahmed, 1964; Weslowski, 1975; Gupta *et al.*, 1980, 1987; Jarowenko and Flechner, 1985; McLaughlin, 1976; Selli *et al.*, 1982; Slaby *et al.*, 1982).

Table Indications, Techniques and Results for Patients Undergoing Ureterocalicostomy

Patient (age in years)	*Aetiology of PUJ obstruction*	*Parenchymal excision*	*Renal artery clamped*	*Estimated blood loss (ml)*	*Peri-operative transfusions*	*Result (months of follow-up)*
TS (42)	Primary PUJ obstruction (intrarenal pelvis)	+	+	800	+	Successful (29)
CF (46)	Surgery for calculi	+	–	350	–	Successful (24)
MS (48)	Surgery for calculi	+	+	1300	+	Failure (renal artery thrombosis requiring nephrectomy)
AD (40)	Surgery for calculi	+	–	900	–	Successful (15)
DK (21)	Failed pyeloplasty	+	–	650	–	Successful (34)
HS (39)	Primary PUJ obstruction (intrarenal pelvis and peripelvic fibrosis)	+	+	1000	+	Successful (47)
JC (54)	Ischaemic allograft ureter; peripelvic fibrosis	–	–	1800	+	Failure due to reobstruction at 4 months

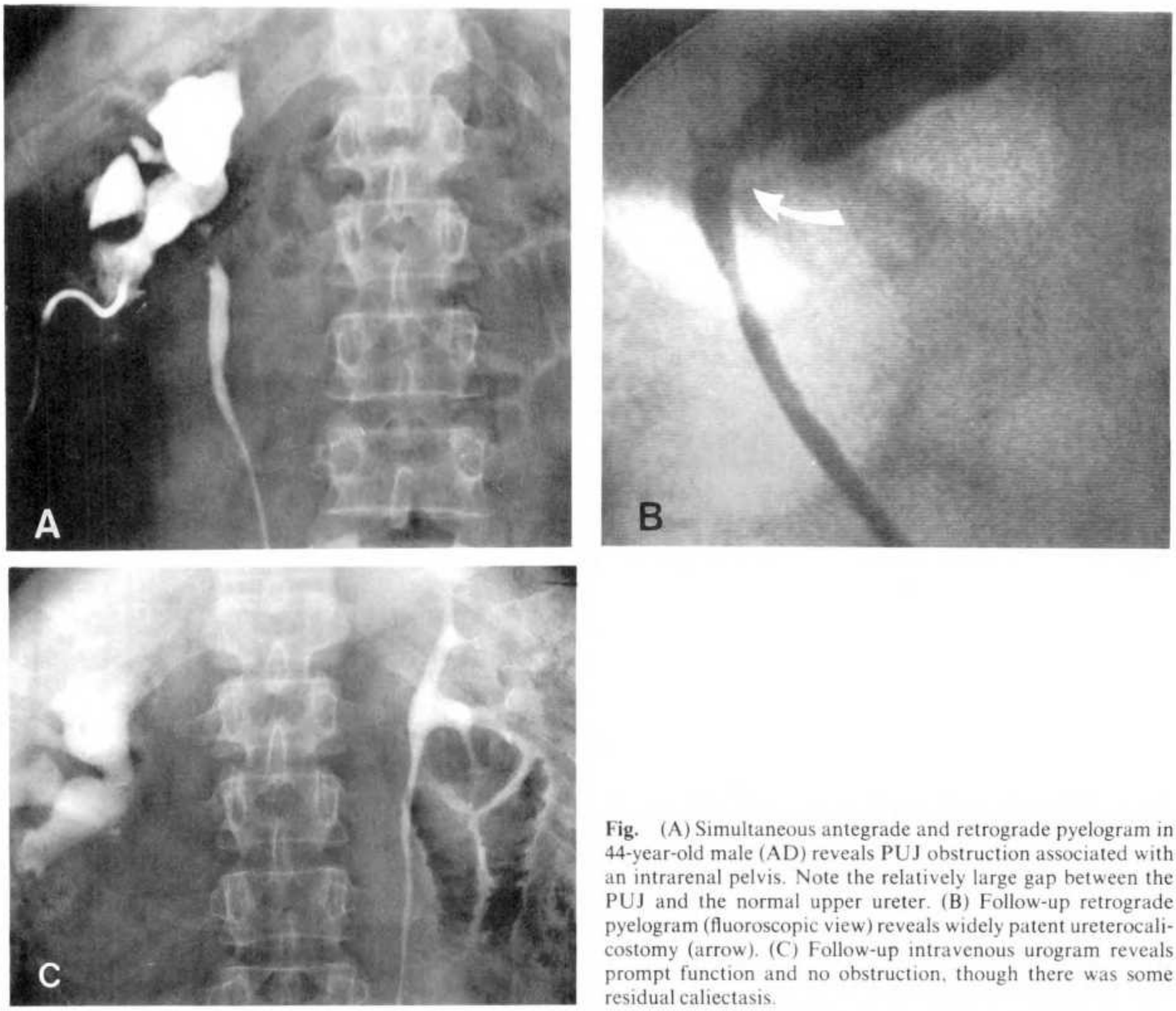

Fig. (A) Simultaneous antegrade and retrograde pyelogram in 44-year-old male (AD) reveals PUJ obstruction associated with an intrarenal pelvis. Note the relatively large gap between the PUJ and the normal upper ureter. (B) Follow-up retrograde pyelogram (fluoroscopic view) reveals widely patent ureterocalicostomy (arrow). (C) Follow-up intravenous urogram reveals prompt function and no obstruction, though there was some residual caliectasis.

Historically, the most common underlying conditions for which ureterocalicostomy was performed were renal lithiasis, congenital PUJ obstruction and renal tuberculosis. It has also been suggested that ureterocalicostomy might be an appropriate primary approach in children with congenital PUJ obstruction in horseshoe kidneys or with profound hydronephrosis (Mollard and Braun, 1980; Levitt *et al.*, 1981).

In our recent experience, the most common problem requiring ureterocalicostomy was fibrosis resulting from previous surgery. The occurrence of PUJ obstruction in a patient with SLE (HS) supports a recent observation that some adults presenting with complicated PUJ obstructions may in fact have systemic sclerosing disease (Baskin *et al.*, 1989).

The most frequently reported complication of ureterocalicostomy is recurrent obstruction (Couvelaire *et al.*, 1964; Selli *et al.*, 1982). Urinary and faecal fistulas have also been reported (Weslowski, 1975; Selli *et al.*, 1982). Our experience confirms the importance of certain technical considerations in preventing these complications. As first suggested by Couvelaire *et al.* (1964), a generous portion of renal parenchyma should be excised from the anastomotic site. It has been suggested that when the overlying parenchyma is thin, a direct anastomosis without excision may be performed (Selli *et al.*, 1982). However, our experience suggests that even if the overlying parenchyma is thin, as it was in JC, a modest excision is advisable for preventing reobstruction.

Fistulas have been a rare complication in the last decade, perhaps due to modern drainage techniques. When feasible, an omental or peritoneal flap may be brought to the anastomosis to improve blood supply during healing. This may help to prevent urinary and faecal fistulas.

We report the first case of renal artery thrombosis occurring in a patient who underwent ureterocalicostomy. This patient, MS, was one of 3 patients in whom the renal artery was clamped intra-operatively. Although the renal artery is often clamped prior to partial nephrectomy when a significant amount of parenchyma is to be excised, its advisability during performance of a ureterocalicostomy has not previously been addressed. Though many factors affect blood loss, it is noteworthy that estimated blood losses and transfusion requirements were not lower in the 3 patients in whom the renal artery was clamped (Table), suggesting that routine clamping may not be necessary. This seems especially true if there is significant hydronephrosis with loss of overlying parenchyma. Therefore, while it may be advisable to expose the renal artery prior to the parenchymal resection, clamping should probably be used only when local control of bleeding is inadequate.

We have found ureterocalicostomy to be a good alternative to pyeloplasty for reconstruction of the pelviureteric junction when extensive scarring or an intrarenal pelvis precludes the use of more conventional techniques. We stress the need for parenchymal excision at the anastomotic site in all cases to prevent reobstruction, though routine clamping of the renal artery prior to this excision is not recommended. Adequate internal and external drainage is essential. When these technical guidelines are observed, the operation can be performed with a satisfactory success rate, considering the already complicated nature of the problem for which it is indicated.

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Endoscopic Transvesical Extramural Ureterolithotomy

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Summary—The technique of endoscopic transvesical extramural ureterolithotomy for calculi impacted in the lower ureter is described. Ten patients are presented in whom calculi could not be extracted using conventional methods; 9 of the 10 calculi were successfully removed using this approach with no long-term complications.

The majority of ureteric calculi will pass spontaneously. Those that do not, and are symptomatic, can usually be removed ureteroscopically or be pushed back into the renal pelvis prior to percutaneous removal or extracorporeal shockwave lithotripsy (ESWL) (Watson, 1987). Should the stone become impacted in the intramural ureter, a simple meatotomy will assist removal, albeit with the risk of subsequent vesicoureteric reflux (Roper and Smith, 1965). However, larger calculi, which have descended into the pelvis, may not enter the intramural ureter and become impacted proximal to the bladder. Although such calculi can usually be removed either ureteroscopically or by the use of ESWL, endoscopic access into the ureter is not always possible. Open methods of removal have been described including the transvesical route (Barnhouse *et al.*, 1973), the transperitoneal approach (Bose and Shaw, 1975) and the retroperitoneal approach (Fox *et al.*, 1965). In the female the transvaginal approach, first described by Emmet in 1879, has more recently been readvocated by O'Boyle and Gibbon (1976). Li and Shapiro (1986) described a technique for removal of calculi impacted in the intramural ureter. We have modified and extended this technique for retrieval of calculi impacted proximal to the intramural segment of the lower pelvic ureter and we report the results in 10 patients treated by this method.

Patients and Methods

During a 2-year period (starting in May 1987) we treated 8 men and 1 woman (mean age 54 years, range 32–76) with calculi impacted at the lower end of the ureter, in whom ureteroscopic removal had been unsuccessful. One further 52-year-old female underwent endoscopic transvesical extramural ureterolithotomy as a planned primary procedure owing to the size of the calculus. In all cases the calculus was either causing significant symptoms or ureteric obstruction warranting intervention. All calculi were situated in the extramural pelvic ureter, at or about the level of the ischial spine. In each case the patient was prepared for ureteroscopy under general anaesthesia with facilities for fluoroscopic X-ray control. After unsuccessful ureteroscopy, an incision was made 3 to 4 cm above the ureteric orifice in the lateral wall of the bladder using a Colling's knife. Using a combination of direct vision and X-ray control, the resectoscope was advanced through the bladder wall and perivesical tissues until the ureter was identified. Surprisingly few large blood vessels were encountered, although great care was required to avoid incising branches of the inferior vesical artery. Once identified, a longitudinal ureterotomy was made and the calculus disimpacted for manipulation back into the bladder and subsequent removal. A ureteric catheter or stent was inserted via the lower ureteric orifice in 4 of the earlier cases, but this was subsequently abandoned as it appeared unnecessary. In all patients a 16 F Foley balloon

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Based on a Poster Demonstration at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

catheter was inserted into the bladder and left on free drainage for between 5 and 10 days (mean 7).

Results

In 9 of 10 patients successful removal was achieved (Table). In 1 case the ureter could not be identified in the perivesical region and the calculus was subsequently removed ureteroscopically. In 1 case pre-operative haemorrhage was controlled by endoscopic diathermy. Post-operative follow-up radiography failed to demonstrate any vesicoureteric reflux or obstructive uropathy in those patients examined. However, in 1 patient a micturating cystogram 2 weeks post-operatively revealed a small perivesical leak with reflux (Fig.). This patient was asymptomatic and therefore received no further treatment. Subsequent cystography 4 weeks later was normal.

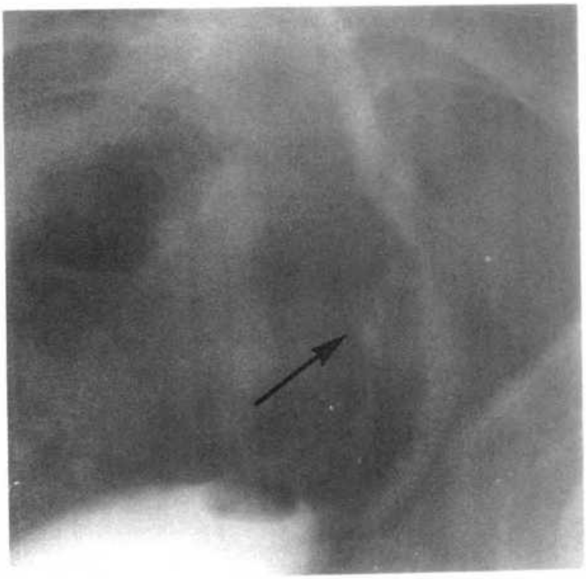

Fig. Micturating cystogram demonstrating small perivesical leak of contrast medium and vesicoureteric reflux.

Discussion

Although the majority of stones in the lower ureter

Table Details of Patients

Case No.	*Age (years)*	*Sex*	*Side*	*Indication*	*Outcome (+/−)*	*Recovery*	*Comment*
1	76	M	R	Failed disintegration of calculus	+	Abdominal pain, 7 days; urethral catheter 7 days; stay 11 days	Perivesical leak on ultrasound
2	50	M	L	Failed ureteroscopy	+	Uneventful stay 7 days; urethral catheter 7 days	
3	50	M	L	Failed ureteroscopy	+	Uneventful stay 6 days; ureteric catheter 2 days; urethral catheter 5 days	IVU normal 6 weeks
4	55	M	L	Failed ureteroscopy	+	Uneventful stay 6 days; urethral catheter 5 days	
5	71	M	R	Failed ureteroscopy	−	Uneventful stay 6 days; urethral catheter 5 days	Ureteroscopic removal subsequent date
6	60	M	R	Failed ureteroscopy	+	Uneventful stay 7 days; urethral catheter 7 days; ureteric stent 4 weeks	
7	52	F	R	Primary approach	+	Uneventful stay 8 days; ureteric catheter 3 days; urethral catheter 7 days	IVU normal 8 weeks
8	32	F	L	Failed ureteroscopy	+	Moderate haematuria; urethral catheter 7 days; stay 8 days	IVU normal 7 weeks
9	47	M	R	Failed ureteroscopy	+	Moderate haematuria; urethral catheter 10 days; stay 13 days	Micturating cystogram; ultrasound normal at 4 weeks
10	47	M	L	Failed disintegration of calculus	+	Uneventful stay 7 days; urethral catheter 6 days	Micturating cystogram; perivesical leak at 2 weeks (asymptomatic); repeat 4 weeks later normal; ultrasound normal

may be removed by conventional ureteroscopy, basket extraction or ESWL, the outcome is not always successful. For the patient expecting an endoscopic procedure, open removal carries both disappointment and increased morbidity. We feel that this technique is therefore a useful additional procedure. Whereas procedures involving the ureteric orifice may result in stenosis or reflux (Roper and Smith, 1965), we have found no radiographic evidence of either in cases where post-operative studies were performed. In all patients the procedure was well tolerated and no long-term consequences have been encountered. We feel that this approach has a valuable place in the management of the impacted ureteric calculus.

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Long-term Results of Colposuspension

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Summary—A series of 102 patients were treated by a technique of colposuspension similar to the Pereyra operation, in which a pair of monofilament sutures were tied over the rectus muscle; 79% of patients (78/99) reviewed 1 year after the operation were continent. During further follow-up (mean 4.5 years) there were 7 late failures, all within 4 years. Kaplan-Meier lifetable analysis showed 69% probability of continence at 5 years. The main factors associated with recurrent or persistent incontinence were detrusor instability (60% incontinent: 9/15) and previous failed colposuspension or multiple vaginal repairs (55% incontinent: 11/20). In the absence of these risk factors 90% of patients maintained continence throughout the follow-up period. This technique has given results at least equal to those reported for the Burch and Marshall-Marchetti-Krantz techniques of colposuspension.

The choice of technique in the surgical treatment of urethral sphincter incompetence has been discussed by Galloway *et al.* (1987). They observed that the choice was influenced by success of the operation in relieving incontinence and post-operative morbidity. They expressed doubts that a Stamey suspension technique could maintain long-term continence because it relied upon only 2 nylon sutures. Mundy (1983) found that the cure rate after 1 year was less using a Stamey bladder neck suspension than using a Burch colposuspension.

The aim of this study was to review the results of a technique of colposuspension with suture placement similar to that of the Pereyra operation. Continence 1 year after the operation and post-operative morbidity were studied, and patients who achieved continence were reviewed to see if this had been maintained in the long term.

Patients and Methods

A total of 102 patients underwent colposuspension between 1979 and 1987, using an open technique in which the full thickness of the vaginal wall was suspended by No. 1 nylon or polypropylene monofilament sutures placed well lateral to the urethra and tied loosely over the rectus muscles. The sutures were inserted through a small incision opening the retropubic space, and placement was guided by a finger in the vagina (Fig. 1A). The position of the sutures relative to the bladder neck was checked endoscopically. The end result was suture placement over the rectus muscles similar to that achieved by Pereyra needle suspension (Fig. 1B).

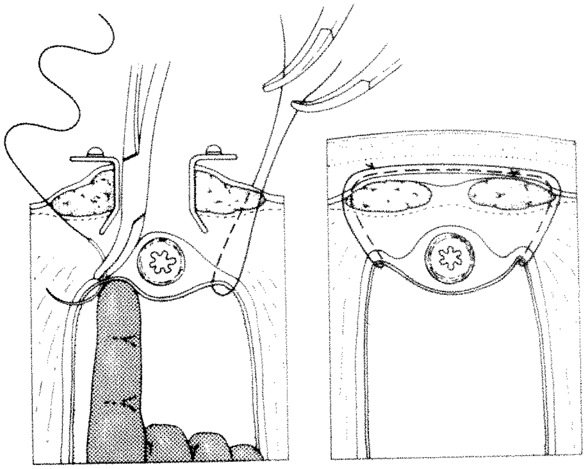

Fig. 1

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No vaginal incision or dissection was made. The monofilament suture lies free in the vaginal lumen initially but becomes buried in the vaginal wall about 2 weeks later. Antibiotics were not routinely used.

The clinical characteristics of the patients are summarised in Table 1. Patients were studied pre-operatively by measurement of resting maximum urethral closure pressure, filling cystometry (without provocation tests) and a voiding study; 15 patients with spontaneous detrusor instability as well as urethral sphincter incompetence were selected for surgery.

Assessment of continence at follow-up interview was subjective. Patients who were "improved" were not regarded as continent. Statistical analysis to construct a Kaplan-Meier probability table and survival curve (Peto *et al.*, 1977) was performed using the BMDP statistical software package.

Results

In the course of the study, 103 operations were performed on 102 patients; 3 were lost to follow-up in the first year and a psychotic patient could not be assessed. The results of 99 operations were therefore available; 78 patients were continent at 1 year. The clinical features of the 21 patients who were not continent at 1 year are shown in Table 2. Pre-operative detrusor instability and multiple previous operations were the main factors associated with failure. One patient broke her suture 3 weeks after the operation but subsequently underwent a further operation with long-term cure.

Table 1 Clinical Features of 102 Patients

Mean age (years)	47
Symptoms	
Stress incontinence alone	24
Frequency, urge and stress incontinence	78
Previous surgery	
Hysterectomy alone	19
One vaginal repair	30
Two vaginal repairs	8
Colposuspension +/− vaginal repairs	12
Detrusor instability	15

Table 2 Clinical Features of 21 Patients with Recurrence of Incontinence within 1 year

Pre-operative detrusor instability	7
Previous multiple operations	9
Post-operative chronic retention	2
Broken suture	2
Chronic cough (1 with pulmonary TB)	2
Radiation cystitis	1
Further radical pelvic surgery	1
Unexplained nocturnal incontinence	1

The number of continent patients available for analysis at annual intervals is shown in Figure 2, with the results plotted as a Kaplan-Meier curve, showing the probability of continence for the whole group at various intervals of follow-up.

There were 7 late failures, all within 4 years of operation; 2 of these 7 failures had detrusor instability pre-operatively. One patient was deceased (incontinent at the time of death) and 1 continent patient was lost to late follow-up, at 3 years.

Morbidity

The main complications associated with the operation (Table 3) were delay in voiding (longer than 10 days in 18%) and excessive wound pain; 27% had pain or discomfort requiring additional visits or treatment, or persisting longer than 2 months. This discomfort disappeared within 4 months. A suprapubic catheter was inserted into the bladder routinely and patients who were unable to void at 10 days were sent home with the suprapubic catheter on open drainage and readmitted for a further trial of voiding at 3 weeks. Only 2 patients ultimately failed to resume normal voiding and are included among the failures. One required a permanent indwelling catheter while the other resumed voiding after a long period of suprapubic catheter drainage but remained incontinent.

The influence on success of the main risk factors, pre-operative spontaneous detrusor instability and previous multiple vaginal repairs or failed colposus-

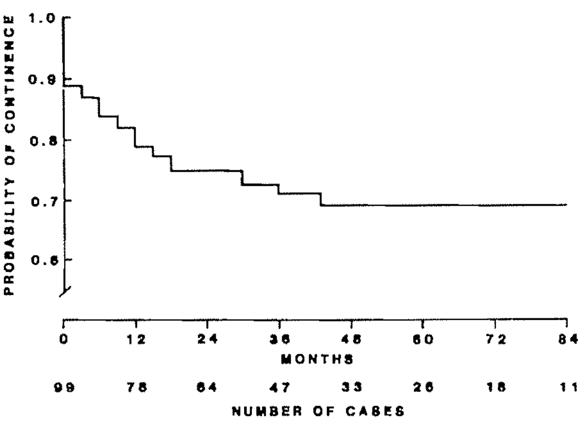

Fig. 2

Table 3 Complications in 102 Patients

Delayed voiding	18
Chronic retention	2
Wound pain and discomfort	27
Wound infection	4
Wound haematoma	2
Incisional hernia	2
Pulmonary embolus	1

Table 4 Risk Factors for Recurrence of Incontinence (Both Early and Late Failures)

	Failed (%)	*No. of patients*
Detrusor instability	60	9/15
Multiple vaginal repairs and/or previous colposuspension	55	11/20
One vaginal repair and stable bladder	23	6/26
No previous surgery and stable bladder	9	4/44

pension, is shown in Table 4. Patients with one previous vaginal repair also appeared to have an increased risk of failure.

Suture breakage or surgical division contributed to failure in 7 patients. Two had early breakage (1 had re-operation), 2 underwent major pelvic surgery with division of the suture, in 2 the suture was removed for wound infection and 1 patient was found to have a broken suture lying loose in the vagina on late follow-up at 4 years. All of these patients had recurrence of incontinence. A chronic cough appeared to be a factor in suture breakage.

Pre-operative symptoms

Almost 80% of patients had mixed symptoms (Table 1) but providing the cystometrogram did not show spontaneous detrusor instability the proportion achieving continence was the same as for those with stress incontinence as the only symptom. Symptoms of frequency and urgency persisted post-operatively in only 20% of continent patients. Age influenced the result, mainly through the higher proportion of patients with failed previous incontinence operations.

Discussion

The early success rate for this study is similar to that in other series (Stamey, 1980; Mundy, 1983; Ashken *et al.*, 1984; Stanton, 1984; Galloway *et al.*, 1987; Spencer *et al.*, 1987; Park and Miller, 1988). All techniques of colposuspension or bladder neck suspension appear to give 90% or better continence at early follow-up for good risk patients, those with a stable bladder undergoing their first operation for incontinence.

The incidence of late recurrence has been less well documented. Spencer *et al.* (1987) studied 95 patients with stable bladders, showing Kaplan-Meier probability curves. Recurrence continued throughout the follow-up period and the same results were obtained with Stamey and Marshall-Marchetti-Krantz operations. Park and Miller (1988) reported a series of Marshall-Marchetti-Krantz operations in patients with stable bladders, with continence falling progressively from 86% of 191 patients at 1 year to 69% of 116 patients at 5 years.

Compared with these studies, the proportion of patients with stable bladders who maintained long-term continence in our series is encouraging.

Comparison of success rates at post-operative annual intervals can be misleading. Results in the form of lifetable curves can be better compared and this statistical method makes more efficient use of data from small numbers of patients (Peto *et al.*, 1977).

The low success rate for patients with instability is disappointing, in spite of efforts to select those patients most likely to benefit. On the other hand, good results were obtained for many patients with urge incontinence. Kulseng-Hansen and Klevmark (1988), using ambulatory monitoring, showed that detrusor instability can be found in most patients with urge incontinence, so it is unlikely that provocation tests to demonstrate a higher proportion of patients with instability would have improved the predictive value of cystometry in our series.

The high failure rate of repeat surgery could be explained by case selection, but gives a strong impression that multiple vaginal repair operations and failed colposuspension cause further impairment of the urethral sphincter mechanism.

We did not find early attempts at needle suspension easy and, like Ashken *et al.* (1984), often entered the bladder; hence the technique of opening the retropubic space was adopted. This had the advantage that the urethra, vagina and bladder neck were fully mobilised, especially important if the patient had undergone previous colposuspension. The end result was suture placement over the rectus muscle as with the Pereyra needle suspension technique. A needle suspension technique can be performed through a smaller incision and in less time, but is not easier because it requires considerable care in suture placement. The results of some series of Pereyra/Stamey operations are marred by a high incidence of post-operative complications and technical failures.

Infection at the vaginal site of the suture, described with the Stamey technique, was not a problem. The sutures were placed as far lateral as possible and did not obstruct the urethra. With experience, the sutures were tied more loosely. The excessive incidence of wound pain experienced early in the series was reduced, and post-operative retention (which related mainly to wound pain or reduced detrusor contractility) was also avoided. Whichever technique of colposuspension is used, avoidance of morbidity from suture breakage, urethral obstruction and wound complications is important.

The superiority of the Burch or Marshall-Marchetti-Krantz suprapubic operations remains unproven. In this study, colposuspension by a simple technique without vaginal incision or dissection, using a pair of monofilament sutures tied over the rectus muscles, has given comparable results with a high probability of long-term continence. The results are highly dependent on case selection, and for good risk cases the possible gain from further variation of technique is limited.

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Clinical Studies on Cell-mediated Immunity in Patients with Urinary Bladder Carcinoma: Blastogenic Response, Interleukin-2 Production and Interferon-γ Production of Lymphocytes

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Summary—Patients with advanced malignant neoplasms have a variety of abnormal lymphocyte functions. We examined the PHA blastogenic response, interleukin-2 (IL-2) production and interferon-γ (IFN-γ) production of lymphocytes in 39 bladder cancer patients and 20 control subjects. Correlation between these parameters was also studied. IL-2 production was measured by ^{3}H-thymidine-labelled CTLL-2 assay, and IFN-γ production was measured by immunoradiometric assay using 2 mouse monoclonal antibodies. As a result, in high stage bladder cancer patients, the PHA blastogenic response, IL-2 production and IFN-γ production were impaired. However, these parameters were not significantly different between low stage bladder cancer patients and control subjects. There was a significant correlation between the PHA blastogenic response and IL-2 production but no significant correlation between the PHA blastogenic response and IFN-γ production.

Immunocompetence of cell-mediated immunity has been found to be impaired in patients with various types of carcinoma. This impairment in cellular immune function has been demonstrated by both *in vivo* tests for delayed-type hypersensitivity reactions and *in vitro* assessment of lymphocyte proliferation and cytotoxicity. For several years, our research group has been studying immunological parameters in patients and animals with bladder carcinoma (Nishio *et al.*, 1979; Wada *et al.*, 1985; Kimura *et al.*, 1986).

Studies in the past 10 years have revealed that the cell-mediated immune response is controlled by a series of soluble factors produced by monocytes and lymphocytes. It has been shown that a monocyte-derived factor, interleukin-1 (IL-1), interacts with antigen- or mitogen-primed helper T cells, leading to their elaboration of interleukin-2 (Breard *et al.*, 1980). IL-2 contributes to the maturation of effector cells such as lymphokine-activated killer (LAK) cells (Grimm *et al.*, 1982), natural killer (NK) cells (Suzuki *et al.*, 1983) and cytotoxic T cells (Gillis *et al.*, 1981), which have the capacity to destroy tumour cells. IL-2 stimulates interferon-γ production (Kawase *et al.*, 1983), which contributes to the induction of cytotoxic T cells (Farrar *et al.*, 1981), activation of macrophages (Hung *et al.*, 1971) and enhancement of NK cell activity (Trichieri and Santoli, 1979). IL-2 and IFN-γ are essential lymphokines for the anti-tumour response. In this study, we examined the PHA blastogenic response, IL-2 production and IFN-γ production of lymphocytes in bladder cancer patients and the relationship between these parameters and the stage of the tumours. The correlation between these parameters was also studied.

Patients and Methods

The study group comprised 39 patients with bladder cancer (mean age 66.6 years). Histological examination of the tumours indicated transitional cell

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carcinoma in all patients. The tumour stage was classified according to UICC (1978). Twenty age-matched control subjects (mean age 66.9 years) whose diagnosis was benign were studied by the same method. Individuals with chronic or acute infection of the urinary tract and those on specific medication were excluded.

Mononuclear cell preparation and culture

Peripheral blood mononuclear cells (PBMC) were separated from freshly drawn heparinised blood by centrifugation over Ficoll-Hypaque gradient. The cells were washed 3 times with RPMI 1640 medium (GIBCO, Grand Island, NY, USA) and suspended at 1×10^6 cells/ml in RPMI medium containing 100 u/ml of penicillin, 50 μg/ml of streptomycin and 10% fetal calf serum (GIBCO) (complete medium). Cell cultures were performed in triplicate in the 96 well microtitre plate (Nunc). Each well contained 2×10^5 mononuclear cells in 200 μl of complete medium, and 10 μg/ml of phytohaemagglutinin P (PHA-P, Difco) was added. The cell cultures were then incubated at 37°C for 72 h in a humidified atmosphere of 5% CO_2 in air. Eighteen hours prior to termination, 0.2 μCi of ^{3}H-thymidine (5 mCi/mmol, Amersham, Japan) were added to each well. The cells were harvested and the incorporation of thymidine into DNA was measured using a liquid scintillation counter. The results were expressed as mean cpm of triplicate wells.

Preparation of IL-2 and IFN-γ supernatants

PBMC were suspended at 1×10^6 cells/ml in the complete medium and cultured with 10 μg/ml of PHA-P for 48 h. The supernatant was centrifuged, passed through a Millipore filter (0.45 μM) and stored at −20°C until testing.

IL-2 assay

The culture supernatants were assayed for IL-2 activity on a cloned CTLL2 cell line. CTLL2 is a murine cytotoxic T cell line that is absolutely IL-2 dependent and does not proliferate in response to PHA-P. The method of Gillis *et al.* (1979) was modified as follows. Duplicate doubling dilutions of 100 μl aliquots of each supernatant were placed in the 96 well microtitre plate. Standard IL-2 aliquots were placed in the plate for comparison. The CTLL2 cells were suspended in the complete medium at a concentration of 1×10^5 cells/ml, and 100 μl aliquots were added to each duplicate supernatant dilution. The microplates were incubated at 37°C in a humidified atmosphere of 5% CO_2 in air. After 20 hours of culture, 0.5 μCi of ^{3}H-thymidine was added to each well and they were cultured for an additional 4 h. ^{3}H-thymidine incorporation was determined by a scintillation counter. The results were expressed as units/ml on the basis of probit analysis.

IFN-γ assay

The culture supernatants were assayed for IFN-γ activity by immunoradiometric assay using 2 mouse monoclonal antibodies (B1 and B3), which are specific for natural and recombinant human IFN-γ. The B1 antibody-coated polystyrene beads were incubated with 200 μl of supernatant in an assay tray at room temperature for 2 h. The beads were then washed with water and incubated with 200 μl of ^{125}I-B3 antibody for 2 h. After washing, the beads were assayed for ^{125}I by a gamma counter according to the manufacturer of the IMRX INTERFERON-GAMMA RIA kit (Centocor Inc., Malvern, PA, USA).

Statistics

All values are expressed as mean ± SD. All values were analysed by one-way analysis of variance and individual comparison was made by the Student-Newman-Keuls test. Regression lines were fitted by the method of least squares.

Results

PHA response of PBMC in bladder cancer patients and control subjects

The mean proliferative response was 17400 ± 6700 cpm for the control subjects, 16700 ± 7300 cpm for the low stage patients and 10900 ± 5300 cpm for the high stage patients. The difference between the controls and the high stage patients and between the low stage patients and the high stage patients was statistically significant ($P < 0.01$, $P < 0.05$). However, the difference between the controls and the low stage patients was not significant (Fig. 1).

IL-2 production of PBMC in bladder cancer patients and control subjects

The mean IL-2 production was 6.6 ± 8.6 units/ml for the control subjects and 6.5 ± 7.7 units/ml for the low stage patients. In contrast, the mean IL-2 production for the high stage patients was 1.1 ± 1.6 units/ml, and this was significantly lower than both that of the controls ($P < 0.05$) and that of the low stage patients ($P < 0.01$) (Fig. 2).

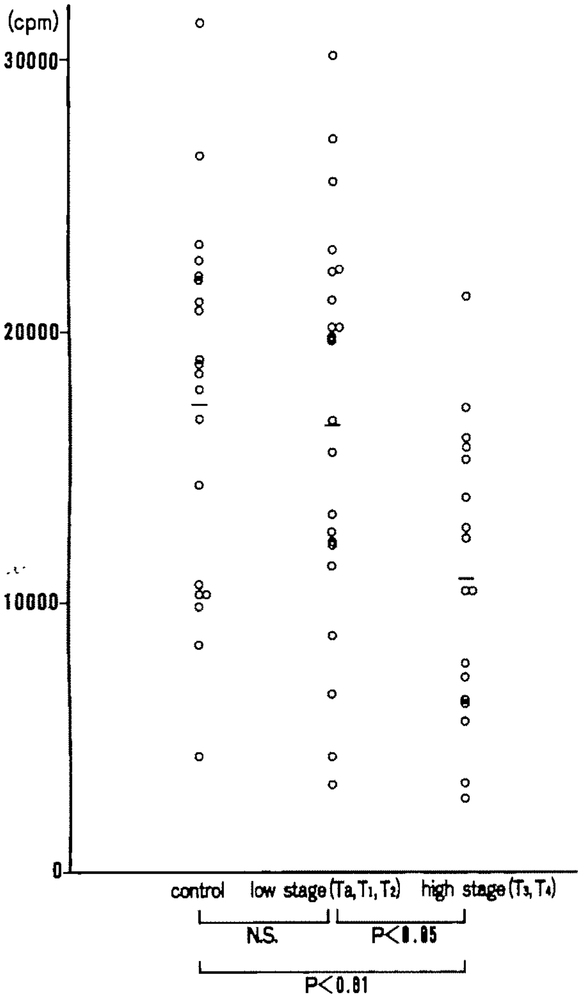

Fig. 1 PHA (20 μg/ml) response of mononuclear cells in control subjects and bladder cancer patients.

IFN-γ production of PBMC in bladder cancer patients and control subjects

The mean IFN-γ production was 102 ± 27 units/ml for the control subjects and 111 ± 30 units/ml for the low stage patients. In contrast, the mean IFN-γ production for the high stage patients was 70 ± 33 units/ml, and this was significantly lower than both that of the controls ($P < 0.01$) and that of the low stage patients ($P < 0.01$) (Fig. 3).

Correlation between PHA response and IL-2 production

There was a significant correlation between the PHA response and IL-2 production ($r = 0.512$, $P < 0.01$) (Fig. 4).

Correlation between PHA response and IFN-γ production

There was no correlation between the PHA response and IFN-γ production ($r = 0.169$, $P = 0.19$) (Fig. 5).

Discussion

Elucidation of the mechanisms responsible for depressed cellular immunity in cancer patients is important. Several factors have been suggested, including intrinsic lymphocyte abnormalities, serum factors and suppressor cells. In the regulation of the cellular and humoral immune response, lymphokines play an essential role. IL-2, which is

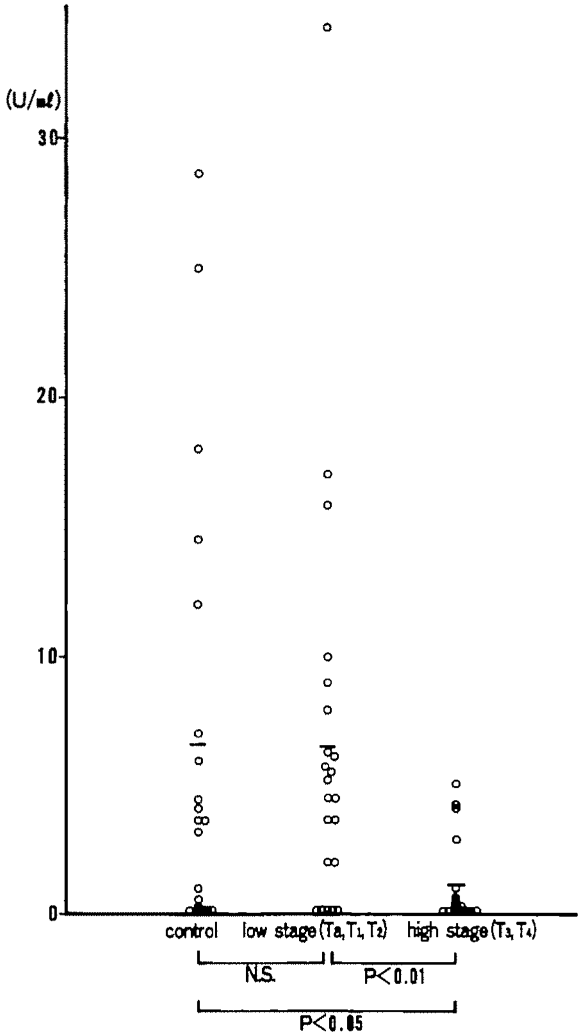

Fig. 2 IL-2 production of monuclear cells in control subjects and bladder cancer patients.

necessary for *in vitro* differentiation and proliferation of effector T cells, can be regarded as one of the most important lymphokines in the regulation of cellular immunity. It has been shown that IL-1 interacts with antigen- or mitogen-primed helper T cells, leading to their elaboration of IL-2 (Breard *et al.*, 1980). It is able to potentiate a variety of cellular cytotoxicities such as LAK cells (Grimm *et al.*, 1982), NK cells (Suzuki *et al.*, 1983) and cytotoxic T cells (Gillis *et al.*, 1981).

IFN-γ, which is another important lymphokine, plays an important role in the regulation or mediation of several important lymphocyte functions. IFN-γ is produced mainly by T cells in response to either antigenic or mitogenic stimulation. IFN-γ is needed for the induction of cytotoxic T cells (Farrar *et al.*, 1981), activation of macrophages (Hung *et al.*, 1971), enhancement of NK cell activity (Trichieri and Santoli, 1979) and regulation of Ia antigen expression on macrophages (Basham and Merigan, 1983). IL-2 and IFN-γ are produced by all T cell subsets, but they are predominantly produced by OKT4 cells (Luger *et al.*, 1982) and OKT8 cells (Von Wussow *et al.*, 1981) respectively.

There have been several investigations concern-

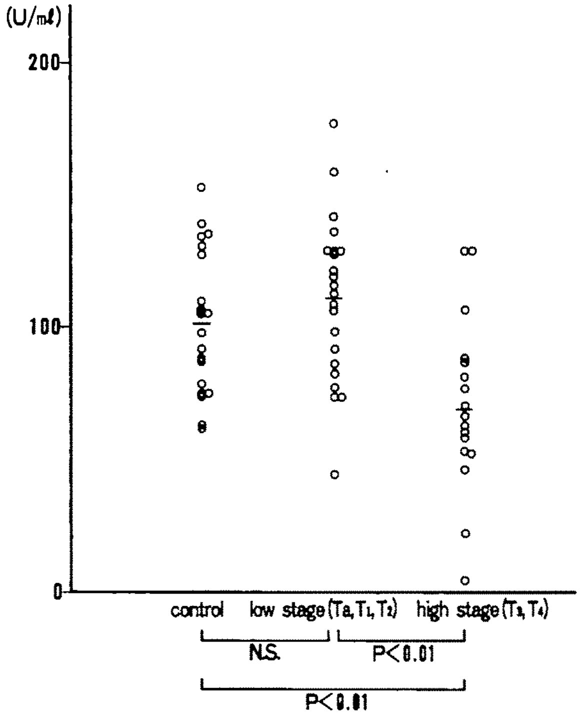

Fig. 3 IFN-γ production of mononuclear cells in control subjects and bladder cancer patients.

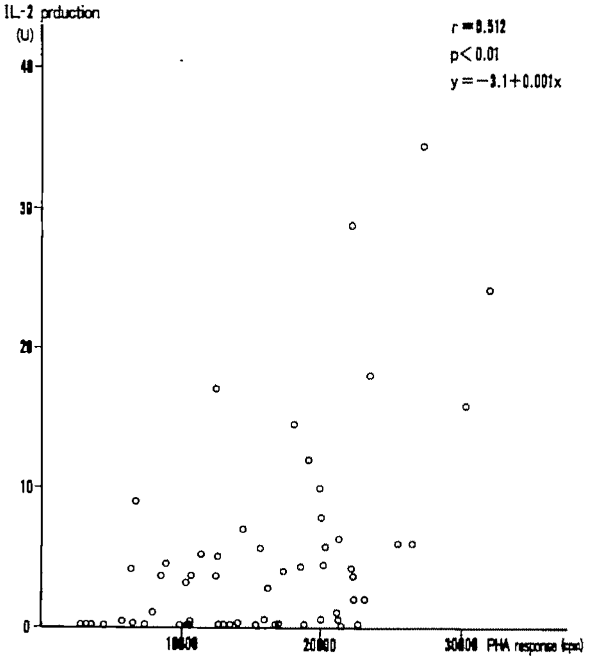

Fig. 4 Correlation between PHA response and IL-2 production of mononuclear cells in control subjects and bladder cancer patients.

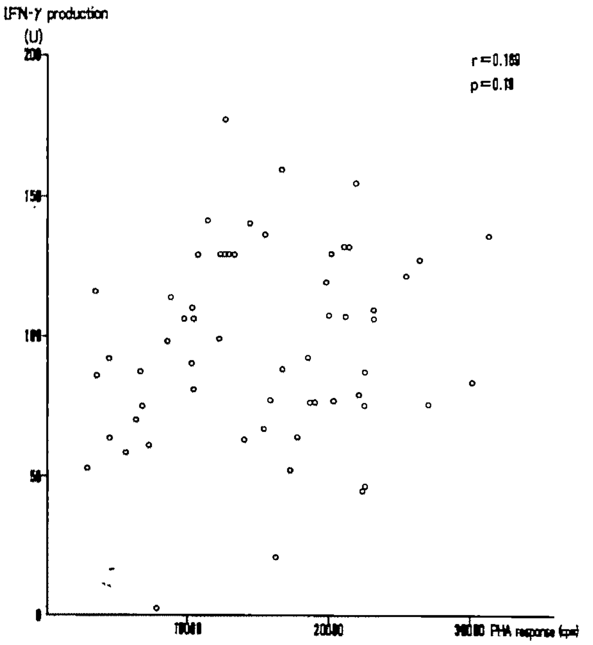

Fig. 5 Correlation between PHA response and IFN-γ production of mononuclear cells in control subjects and bladder cancer patients.

ing IL-2 and IFN-γ production by lymphocytes in patients with malignancy. Most of these reports have indicated that cancer patients are unable to generate normal levels of IL-2 (Nakayama *et al.*, 1983; Monson *et al.*, 1986; Wanebo *et al.*, 1986) and IFN-γ (Kusugami *et al.*, 1984; Rassiga-Pidot and McIntyre, 1974). Our results showed that the capacity to produce IL-2 and IFN-γ was normal in low stage cancer patients but depressed in high stage cancer patients. The mechanisms responsible for the abnormal production of lymphokines by lymphocytes derived from cancer patients remain unknown. One possibility could be that cancer patients have decreased percentages of lymphokine producer cells and/or increased percentages of suppressor cells (Chouaib and Fradelizi, 1982; Burger *et al.*, 1984; Rey *et al.*, 1984). In addition, it has been reported that tumour cells may release an immunosuppressive factor (Hersey *et al.*, 1983). Insufficient levels of lymphokines may cause the depression of cellular anti-tumour defence. The reduced effects of IL-2 may be a reason for the abnormality in LAK cells, NK cells and cytotoxic T cells. In addition, the reduced IFN-γ may depress NK cell and macrophage activity against tumour cells.

When the correlation among the parameters which indicate cellular immunity was studied, there was a correlation between the PHA blastogenic response and IL-2 production. However, IFN-γ production did not correlate with the PHA blastogenic response. IFN-γ production may be a different parameter to assess the functions of lymphocytes in cancer patients.

Several reports have demonstrated that IL-2 regulates IFN-γ secretion (Handa *et al.*, 1983; Kawase *et al.*, 1983). Impaired IL-2 production may lead to the low level of IFN-γ production. However, in our study, there was no correlation between the production of IL-2 and IFN-γ. Our results suggested that IL-2 and IFN-γ are parameters of cellular immunity which are independent of each other, and that the production of both IL-2 and IFN-γ was suppressed in high stage cancer patients. Cellular immunity is strikingly depressed, especially in patients with advanced tumours. Recently, recombinant IL-2 (Rosenberg *et al.*, 1985; Lotze *et al.*, 1986) and recombinant IFN-γ (Foon *et al.*, 1985; Takaku *et al.*, 1987) have been used in cancer treatment as one of the biological response modifiers (BRM). Further studies on the mechanisms of immunosuppression in tumour progression should provide some insight into clinical immunotherapy.

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Transferrin Receptor Expression in Primary Superficial Human Bladder Tumours Identifies Patients who Develop Recurrences

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Summary—A group of 65 patients with superficial bladder carcinoma was followed for 2 years and tumour recurrence rate was correlated both with transferrin receptor status of the initial primary tumour and with the results of voided urine cytology. Nine of 24 patients with transferrin receptor negative tumours had recurrences compared with 30 of 41 patients with transferrin receptor positive tumours. This difference was highly significant.

Urine cytology at presentation was also predictive of further tumour formation: of 30 patients who were transferrin receptor positive and had positive urine cytology, 25 developed recurrences.

Diagnosis of bladder cancer is now well recognised as detection of a tumour in a patient with an "at risk" urothelium. Between 50 and 70% of patients with superficial bladder cancer will develop subsequent bladder tumours and 10 to 20% of these will progress to invade muscle (Gammelgaard and Sorensen, 1978; Heney *et al.*, 1982; Abel, 1988a), resulting in the description of this condition as a polychronotopic diathesis (Prout, 1980).

The identification of patients with superficial bladder cancers most likely to develop recurrences is based on morphological features. Patients with large (>3 cm), multiple and high grade tumours, especially in the presence of lamina propria invasion (pT1) and in association with abnormal findings observed from cold cup biopsies to sample field changes, are considered more prone to develop recurrences (Schade and Swinney, 1968; England *et al.*, 1981; Lutzeyer *et al.*, 1982; Pocock *et al.*, 1982; Dalesio *et al.*, 1983; Heney *et al.*, 1983; Wolf and Hojgaard, 1983; Abel *et al.*, 1988). However, variability in histological grading and pathological staging—even by the same pathologists—is well recognised and illustrates the difficulties with subjective predictors in this disease (Ooms *et al.*, 1983; Abel *et al.*, 1988b).

Several other characteristics, such as red cell antigen status and ploidy, have been examined in an attempt to improve assessment and more accurate diagnosis. In this context, we selected transferrin receptor (TFR) expression as a marker in human bladder tumours. TFR expression, detected by means of light microscopy and considered to be a marker of proliferative activity (Sutherland *et al.*, 1983), has been studied previously in 68 primary transitional cell bladder carcinomas and 22 control sections. TFR positive staining was seen in 6/19 (31.6%) grade I, 22/30 (73.3%) grade II and 15/19 (78.9%) grade III tumours, with a similar increase in positivity with increasing pathological stage. None of the control sections stained positively (Seymour *et al.*, 1987).

We report the results obtained from 65 patients whose original superficial bladder cancers were stained for TFR and who have been followed up for 2 years in the urology units at the Royal Brisbane and Toowoomba General Hospitals.

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Patients and Methods

Tissue specimens were obtained from 65 patients, 55 males and 10 females with a mean age of 69.5 years (range 33–92), who had had transurethral resection of their primary bladder tumours; 60 patients had voided urinary cytological examination, and bacteriological examination was a routine in all patients prior to diagnostic cystourethroscopic inspection.

These patients were followed up for 2 years from the time of their initial histological diagnosis and check cystourethroscopies were carried out approximately every 3 months. All of these procedures were performed by registrar and consultant urological staff at Royal Brisbane Hospital and consultant urological staff at Toowoomba General Hospital. Voided urine specimens were obtained for cytological and bacteriological examination prior to these endoscopic bladder assessments.

Tissue preparation

Each specimen was divided into 2, with 1 part being sent for routine histopathological examination (formalin fixed, paraffin embedded and stained with haematoxylin and eosin). The other part was immediately embedded in OCT, quenched in liquid nitrogen and stored at −70°C until used. Five micron sections were cut, air dried for 2 h, fixed for 5 min in equal parts chloroform/acetone at room temperature, then wrapped in plastic film before storage at −20°C until used. A haematoxylin and eosin slide was made from each specimen to confirm the presence of tumour. Histological grading and staging were performed on paraffin sections.

Immunohistology

Indirect immunofluorescence and avidin-biotin immunoperoxidase labelling were carried out as described by Poulter *et al.* (1982). The staining and labelling routine using OKT9 (orthomune) as the first layer antibody has been described by Seymour *et al.* (1987). Control sections included the use of PBS, normal mouse serum and an irrelevant monoclonal antibody (FN4/BA4−) which reacts with an antigen on *Fusobacterium nucleatum* (Walsh *et al.*, 1985) in place of the primary antibody.

Histological assessment

Histological grading was performed by G.M.S., using the grading system described by Pauwels *et al.* (1988), in which grade II lesions are divided into IIa and IIb on the basis of polarity as an indicator of likelihood of recurrence formation. The UICC (1978) pathological staging system was used. Immunohistological assessment was performed by G.J.S. and all cytological studies were undertaken by G.R.W.

Results

Tables 1 and 2 detail the relationship of TFR+ status to the presence or absence of recurrences of grade and pathological stage. Grade II has been categorised as IIa and IIb (Pauwels *et al.*, 1988). Table 1 shows that 66% of the recurrences in patients with pTa initial tumours were TFR+, which compared with a value of 39% for non-recurrences. In the case of tumours which involved lamina propria, the corresponding values were 89 and 66% respectively (Table 2); 77% of patients who had recurrences had TFR+ initial tumours compared with 42% of those with TFR+ initial lesions in whom no further tumours were seen. Table 3 illustrates the high correlation rate of TFR+ in the original lesion to subsequent tumour formation over a 2-year period. This is highly significant using the chi^2 test with the Fischer variant ($P<0.001$).

Voided urinary cytology results were regarded as positive if reports stated "cytological evidence of transitional cell carcinoma" or "atypical cells suspicious of transitional cell carcinoma". Positive cytology immediately prior to cystoscopic diagnosis of the initial tumour correlated strongly with a tendency to subsequent recurrence formation ($P<0.01$) and was much more predictive in this regard than the cytological result obtained imme-

Table 1 Stage pTa Tumours

Grade	*Recurrences*	*TFR+*
I	7 yes*	3*
(n=17)	10 no	4
IIa	7 yes†	4
(n=16)	9 no	3
IIb	6 yes§	6§
(n=8)	2 no	0
III	1 yes‡	1‡
(n=3)	2 no	2
Total	21 yes	14
(n=44)	23 no	9

* = Thiotepa at diagnosis: doxorubicin at 12 months.
† = Doxorubicin following diagnosis: BCG at 12 months.
‡ = Radiotherapy following diagnosis: BCG at 21 months.
§ = Radical radiotherapy at 3 months.
(Each symbol equates with 1 patient who had the described adjuvant therapy).

Table 2 Stage pT1 Tumours

Grade	*Recurrences*	*TFR+*
I (n=3)	2 yes 1 no	0 1
IIa (n=3)	3 yes 0 no	3 0
IIb (n=10)	9 yes 1 no	9 1
III (n=5)	4 yes*† 1 no	4*† 0
Total (n=21)	18 yes 3 no	16 2

* = Radiotherapy at diagnosis.
† = Radiotherapy following diagnosis: BCG at 21 months.
(Each symbol equates with 1 patient who had the described adjuvant therapy).

Table 3 Time of Recurrence (with Number TFR+) over 2 Years

	1	*2*	*3*	*>3 Recurrences*
pTa				
Grade I (n=7)	3 (+)	2	0	2 (+ +)
Grade IIa (n=7)	3 (+)	3 (+ +)	0	1 (+)
Grade IIb (n=6)	2 (+ +)	2 (+ +)	2 (+ +)	0
Grade III (n=1)	0	1 (+)	0	0
pT1				
Grade I (n=2)	2	0	0	0
Grade IIa (n=3)	3 (+ + +)	0	0	0
Grade IIb (n=9)	1 (+)	1 (+)	4 (+ + + +)	3 (+ + +)
Grade III (n=4)	3 (+ + +)	0	0	1 (+)

+ = TFR+ status per initial tumour.

diately before diagnosis of the recurrence; 39 patients had 1 or more recurrences over the 2-year period and 34 of these had cytology performed immediately before diagnosis; 26 (76%) had positive cytology (18 definite, 8 atypical). Of the 26 patients who did not have 1 tumour recurrence, 13 (50%) (6 definite, 7 atypical) had positive cytology initially. Twenty-five patients had both TFR+ tumours and positive initial cytology, and of these 20 (80%) had 1 or more recurrences. In the TFR− group, 12 patients had initial positive cytology and 4 of these (33%) had 1 or more recurrences. The difference between these 2 groups was significant ($P<0.01$). However, of the TFR− tumour patients, none had more than 2 recurrences in the 2-year period, 6 having only 1 (Fig. 1). On the other hand, of the 41 patients with TFR+ tumours, 31 had 1 or more recurrences and half of these had 3 or more recurrences (Fig. 2).

Twenty patients had multiple tumours at the time of diagnosis and 12 of these were associated with 1 or more recurrences. Of the 6 TFR− patients with multiple original tumours, only 1 (16%) had recurrences. In the TFR+ group, 11 of the 14 patients with multiple tumours (78%) had 1 or more recurrences in the 2-year period. Thus multiple tumours at the time of initial diagnosis did not correlate well with a tendency to recurrence formation, but, in the context of TFR+, there was a very strong correlation.

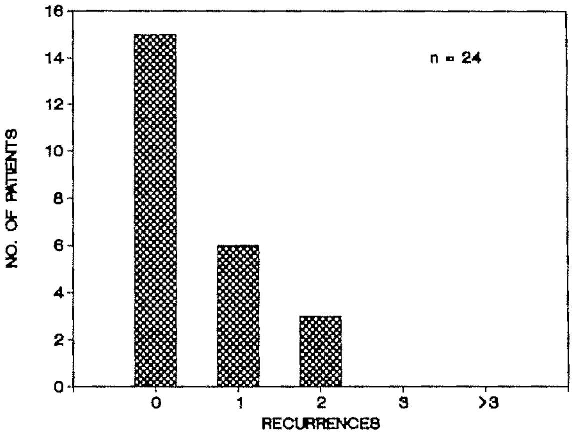

Fig. 1 Recurrences in patients with TFR− tumours.

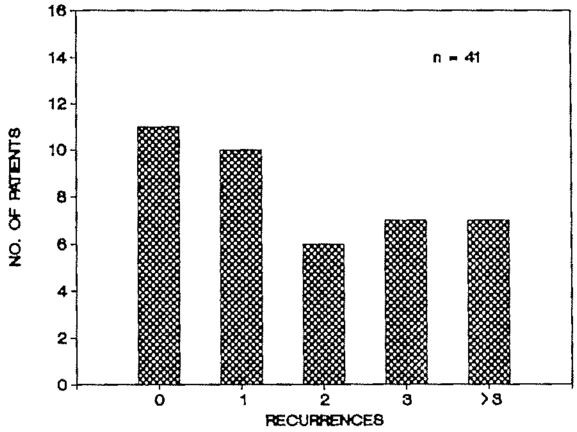

Fig. 2 Recurrences in patients with TFR+ tumours.

Discussion

The requirement by clinicians for reliable, practical indicators of innate urothelial behaviour has been associated with several seemingly disparate lines of research to identify markers which indicate recurrence formation and tumour progression. These include investigation of oncogenes, chromosomal analyses, ploidy, morphometric studies and changes in antigen expression (Lange *et al.*, 1978; Ooms *et al.*, 1981; Summers *et al.*, 1981; Klein *et al.*, 1982; Fujita *et al.*, 1984; Goudarzi *et al.*, 1984; Hadjissotiriou *et al.*, 1985). Despite observable differences reflecting various aspects of cell disturbances, none has been accepted as a sufficiently reliable predictor in individual patients to warrant routine clinical use. Consequently, 3-monthly check cystourethroscopies remain the rule for patients with superficial bladder cancer, intervals between inspections increasing with negative cystourethroscopic, histological and cytological findings.

In this study there was a highly significant difference between TFR− and TFR+ tumour patients with respect to the likelihood of new tumour formation during the 2-year period ($P<0.005$). All 6 patients who had adjunctive treatment in the form of supervoltage radiotherapy and/or intravesical therapy had recurrences. Radiotherapy is recognised as having little effect on the predilection for new tumour formation in this disease (Caldwell *et al.*, 1967; Buschke *et al.*, 1968; Van Der Werf-Messing, 1971; Sawczuk *et al.*, 1988) and intravesical therapy was less than totally effective in this group. Thus determination of TFR expression of the initial bladder tumours proved highly predictive.

The detection of abnormal voided urinary cytology immediately prior to diagnostic TURBT complemented TFR status predictability ($P<0.01$) to identify patients particularly likely to have further bladder tumours and for whom close surveillance was most important. An interesting observation was that the initial cytological status was more predictive than that obtained immediately prior to diagnosis of recurrences, so that the combination of TFR status of the original tumour and cytological findings at this time appeared most prognostic in terms of subsequent urothelial behaviour.

Although apparently normal urothelium was not biopsied as a matter of course during the 2-year period, suspicious areas were obtained for histological scrutiny as a routine. When recurrences were diagnosed there was histological confirmation of tumour in 78% of cases. Thus there was good pathological correlation of the diagnoses. The 8% (5/65) progression rate is a little lower than that normally reported (England *et al.*, 1981; Dalesio *et al.*, 1983; Heney *et al.*, 1983), but if considered in terms of TFR positivity, the progression rate increases to 12% (5/41).

An unexpected finding was that the number of tumours at initial diagnosis did not relate strongly to the recurrence rate. In terms of TFR status, however, there was a good correlation, with 78% of patients with multiple tumours and TFR positivity having recurrences. Considerable importance is placed on the subjective indices of tumour size and number of lesions with respect to likelihood of recurrence formation. However, a false impression of the number of initial individual tumours may result from the merging of lesions in close proximity to form coalesced larger tumours, so that size and number are not totally independent predictive parameters. The fact that primary tumour size was not documented consistently in this series is, therefore, probably not of great consequence.

During the 2-year period, atypical but not definitely malignant cytological results were reported on only one occasion without detection of bladder tumours at subsequent cystourethroscopies. In this patient, further urinary cytology results were also normal, this finding being well within the recognised limitations in accuracy of voided urinary cytology (Murphy *et al.*, 1984; Mueleman and Delaere, 1988). Although voided cytology may serve as a random sampling of urothelium in the absence of an overt bladder tumour, this is certainly not the case in the presence of an identifiable tumour, and the relationship of the initial results with TFR status in prediction is intriguing.

Pauwels *et al.* (1988) described their experience with an expanded grading system, dividing grade II lesions into IIa and IIb based on nuclear polarity which they found related to predisposition to recurrence formation. In this study there was a trend in the TFR positive patients for those with 3 or more recurrences to be IIb at diagnosis, but these numbers are small and not statistically significant. Similarly, the numbers studied were too few to enable any valid analysis of TFR positive staining into the 3 patterns previously reported (Seymour *et al.*, 1987). With the accrual of further patients to this study, the significance of these patterns may become apparent.

Although patients with superficial bladder cancer constitute a group predisposed to further tumour formation, most patients—even those with multiple recurrences—have more negative than positive check cystourethroscopies. Despite a lessening of morbidity with the use of flexible cystoscopes, these procedures continue to have a considerable socioeconomic impact. Therefore, if the frequency of these examinations can be reduced without any untoward effect on patient welfare, a more productive allocation of endoscopic services should be possible (Morrison *et al.*, 1984; Mueleman and Delaere, 1988).

Maximising pertinent information at the time of the initial presentation by determining the TFR status of primary tumour, together with the histological classification incorporating 2 grade II categories as proposed by Pauwels *et al.* (1988) as well as voided urinary cytology at this time, should provide a greater level of confidence for determining the frequency of future check cystourethroscopies. Clinical judgement will continue to remain the most important factor in determining future management of patients. TFR status, which is easily gleaned from a frozen section specimen, promises to complement standard histopathology and cytology (Morrison *et al.*, 1984; Mueleman and Delaere, 1988) in helping to make these decisions more effectively.

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Prediction of Response to Radiotherapy in Invasive Bladder Cancer

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Summary—The original pre-treatment histological sections from 125 patients with invasive (T2/T3) transitional cell bladder cancer treated by radical radiotherapy were studied; 63 tumours responded completely to radiation and 62 did not; 55 of 72 tumours containing areas of squamous metaplasia and 27 of 36 staining for beta-human chorionic gonadotrophin failed to respond to radiotherapy; 26 of 28 tumours showing both squamous metaplasia and beta-human chorionic gonadotrophin did not respond to radiation, whereas 40 of 45 tumours without either of these features responded.

The DNA ploidy of 86 tumours in the series was measured by flow cytometry; 11 of 27 aneuploid and 30 of 59 diploid tumours responded to irradiation.

Squamous metaplasia and beta-human chorionic gonadotrophin in bladder cancer indicate resistance to radiotherapy but DNA ploidy does not.

The mortality rate from invasive bladder cancer, however treated, remains unacceptably high. In this department, patients with invasive (T2/T3) transitional cell carcinoma of the bladder have hitherto been offered a course of radical radiotherapy to a dose of 5500 cGy as described by Hope-Stone (1986). Salvage cystectomy is reserved for those who fail to respond, as judged by the cystoscopic and biopsy appearances 6 months after completion of radiation, provided the patient has not developed distant metastases and is fit to withstand the operation. A review of patients treated in this way between 1965 and 1974 revealed 2 distinct groups of invasive bladder cancers—those that did and those that did not respond to radiotherapy. If the bladder cancer disappeared after the initial course of treatment, the patients did quite well; if the cancer did not disappear, they did very badly (Blandy *et al.*, 1980).

Despite the criticism that cystectomy was performed in only 8% of the series and the anomaly that patients with T3 disease had an apparently better survival than those with T2 cancers, we persisted in this treatment policy. Over the next decade, analysis of results of patients treated from 1974 to 1985 showed the same phenomenon—although there was a slight improvement in the figures, there was the same stark difference. In the fortunate group where there was a complete response to radiotherapy, there was a 58% 5-year survival rate and only 20% developed a relapse requiring cystectomy. In sharp contrast, the other half, who showed no response to radiation, had a 5-year survival rate of only 18%, although this figure was increased to 47% by salvage cystectomy (Jenkins *et al.*, 1988). The crucial question, therefore, is how these 2 populations of cancers can be distinguished from one another.

In recent years there has been considerable interest in the measurement of the deoxyribonucleic acid (DNA) content and its association with prognosis in a large range of tumours (Friedlander *et al.*, 1984). Dyes, such as ethidium bromide and propidium iodide, bind to double stranded nucleic acids and, following removal of ribonucleic acid, the degree of staining is proportional to the amount of DNA in the cell. The DNA content of individual cells may then be calculated—most conveniently

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Read at the 45th Annual Meeting of the British Association of Urological Surgeons in St Helier, June 1989

by automated flow cytometry that enables the examination of approximately 1000 cells every second (Taylor, 1980). This analysis results in representative DNA histograms, the channel number being a reflection of the relative fluorescence intensity and directly proportional to the DNA content. It is conventional to divide tumours into 2 broad groups: "diploid" when the DNA content of the cells is normal (Fig. 1) and "aneuploid" when the content is clearly abnormal (Fig. 2).

The ploidy of transitional cell carcinomas of the bladder has been studied using either cytological washings (Hadjissotiriou *et al.*, 1987) or paraffin-fixed tissue sections (Blomjous *et al.*, 1988). Some have reported a strong correlation of ploidy with tumour grade and stage (Tribukait *et al.*, 1982; Wijkstroem *et al.*, 1985) as well as with survival (Blomjous *et al.*, 1988). These findings prompted us to investigate whether the ploidy of invasive bladder tumours was related to the response to radiotherapy.

We had previously found that the presence of squamous metaplasia in tissue sections of bladder cancers and the expression by the tumour of beta-human chorionic gonadotrophin (beta-hCG) indicated a lack of response to radiation (Martin *et al.*, 1989a, b). This communication describes the findings in patients who presented from 1980 until the end of 1987 and correlates these histological features with DNA ploidy.

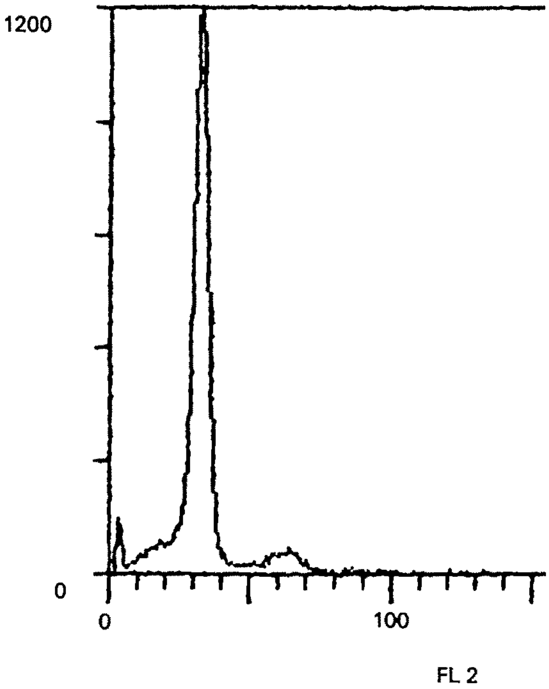

Fig. 1 DNA histogram of diploid tumour showing a distinct G0/G1 peak (channel 30) and a smaller G2 peak (channel 60).

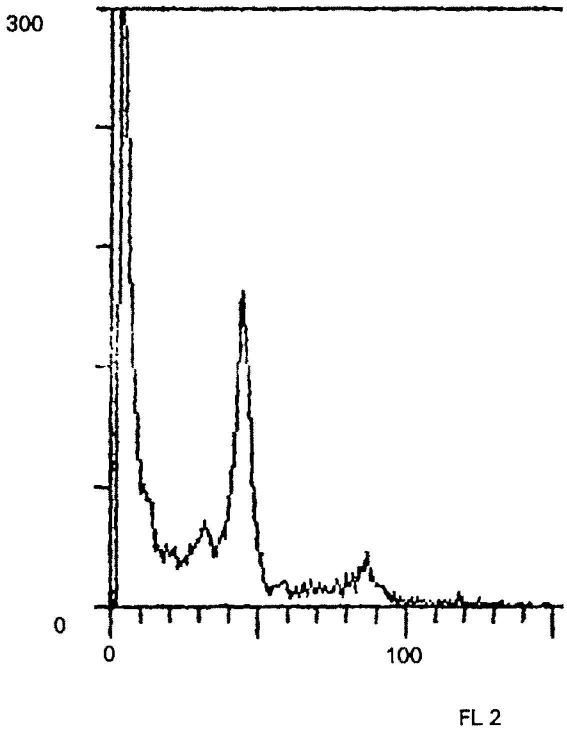

Fig. 2 DNA histogram of aneuploid tumour showing a small G0 peak (channel 30) and a large S-phase (aneuploid) peak at channel 45.

Methods

The study comprised the original pre-treatment histological specimens from 125 patients with invasive transitional cell carcinoma of the bladder who presented to the Department of Urology between 1980 and 1987, obtained from the files of the Pathology Department. Sections, stained in haematoxylin and eosin, were reviewed independently by a team of pathologists unaware of the clinical outcome and the presence or absence of squamous metaplasia recorded (Fig. 3). From 1 to 9 blocks were available in each case (mean 2.9). All 125 sections were also stained with an indirect immunoperoxidase technique for the beta sub-unit of hCG (Fig. 4). The methods were detailed by Martin *et al.* (1989a, b). The technique of radiotherapy and the criteria used to determine complete clinical response were as described previously (Jenkins *et al.*, 1988).

In addition, sufficient tissue was available to analyse the DNA content of 86 tumours. The

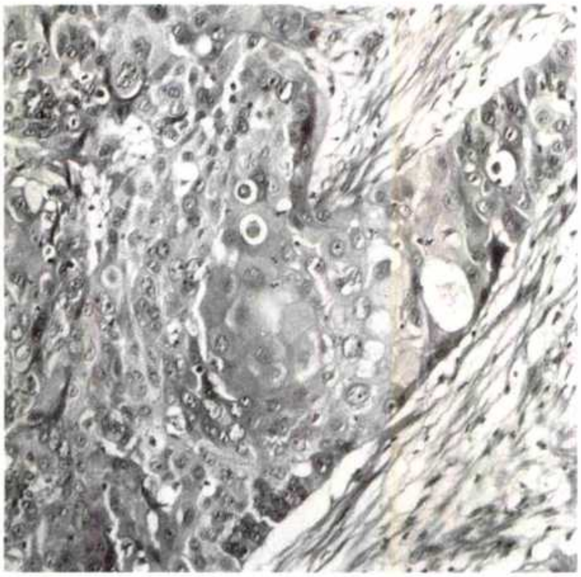

Fig. 3 Poorly differentiated transitional cell carcinoma showing island of squamous metaplasia (H and E × 400).

original paraffin embedded sections were prepared according to the method described by Hedley *et al.* (1983) and the resulting suspension passed through a flow cytometer (FACS II Becton-Dickinson). The DNA content of 10,000 cells per section was counted and the results analysed using standard DNA cell-cycle software.

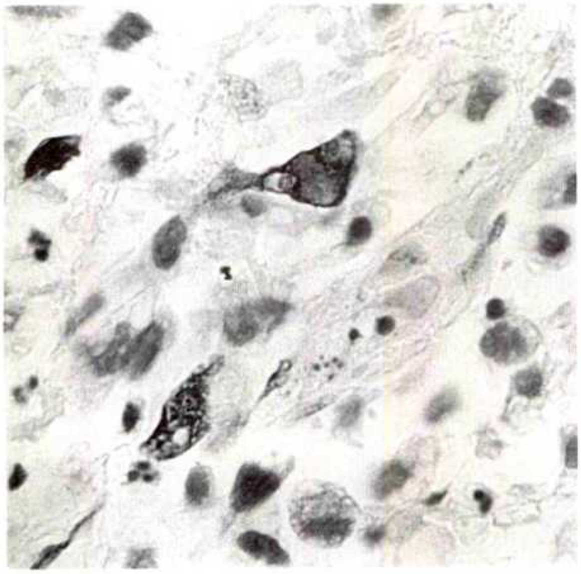

Fig. 4 Indirect immunoperoxidase positive stain for beta-hCG in transitional cell carcinoma (× 400).

Results

The mean age of the patients was 69.4 years (range 33–85); 96 were male and 29 female; 115 tumours were classified as G3 and 10 G2. Squamous metaplasia was present in 72 tumours (58%) and 36 (38%) stained positive for beta-hCG.

All patients were treated with a course of radical radiotherapy: 63 tumours responded completely as judged by the cystoscopic and biopsy appearances 6 months after completion of the course of radiation and 62 did not; 55 of 72 tumours (76%) showing areas of squamous differentiation (Fig. 5) and 27 of 36 (75%) staining for beta-hCG (Fig. 6) failed to respond to radiotherapy. Of 28 tumours which expressed both squamous metaplasia and beta-hCG, 26 (93%) failed to respond to radiation; in contrast, when neither of these features was present, 40 of 45 tumours (88%) responded.

Analysis of the flow cytometry data showed that 27 tumours (32%) were aneuploid and 59 (68%) were diploid; 11 of 27 aneuploid (41%) and 30 of 59 diploid tumours (51%) responded to radiation; 53 of the 86 sections (62%) subjected to DNA estimation showed areas of squamous metaplasia: 16 were aneuploid and 37 diploid. Twenty-five of the 86 tumours (29%) stained positively for beta-hCG: 12 were aneuploid and 13 diploid. Squamous differentiation was present, therefore, in 60% of aneuploid and 63% of diploid tumours. In contrast, 44% of aneuploid but only 22% of diploid tumours expressed beta-hCG.

Discussion

It is well known that bladder tumours, like other tumours, may sometimes express beta-hCG (Rodenburg *et al.*, 1985). When associated with squamous metaplasia, however, the finding that this is such a sinister feature in the prognosis of bladder cancer has not been previously recognised.

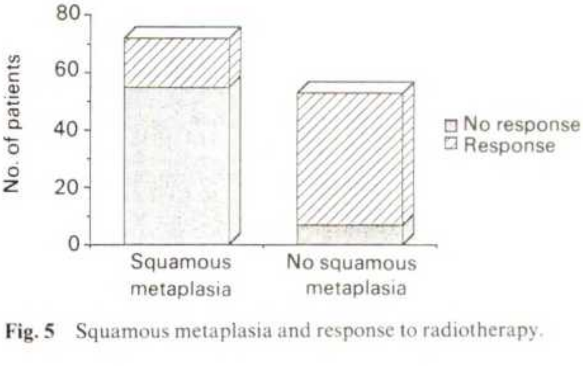

Fig. 5 Squamous metaplasia and response to radiotherapy.

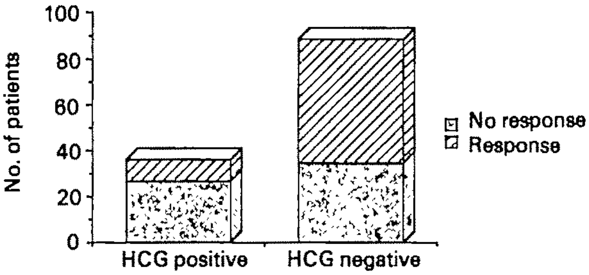

Fig. 6 HCG expression and response to radiotherapy.

The results of this series suggest that the presence of squamous differentiation and the expression of beta-hCG signify radioresistance. It is not yet known whether bladder cancers showing these features will also fare badly when treated by total cystectomy or chemotherapy. Squamous metaplasia and positive staining for beta-hCG may just be an index of wickedness rather than an index of radioresistance. Unexpectedly, they are not related to tumour ploidy.

When sections neither show squamous metaplasia nor stain for beta-hCG, the tumour is very likely to respond to radiation and cystectomy may reasonably be held in reserve.

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Local Microwave Hyperthermia in the Treatment of Benign Prostatic Hypertrophy

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Summary—Local deep microwave hyperthermia has been introduced recently for the treatment of benign prostatic hypertrophy (BPH). We report the results of treatment in 114 patients divided into 2 groups. The first group included 83 patients with severe obstructive symptoms. Although some improvement was found in the scoring of both subjective and objective parameters, the number of patients benefiting was small, with only 28% showing improvement in both parameters. Approximately 50% reported subjective improvement but in only 25% was this significant. In 42% there was objective evidence of improvement. Prostatic volumes did not change as a result of treatment.

The second group comprised 31 patients with indwelling catheters because of acute urinary retention. After treatment, 19 patients (61%) were able to dispense with the catheter.

The difficulties of interpreting an open trial of treatment for BPH and assessing its impact on objective parameters and symptomatology are discussed. Our results should be regarded cautiously in view of these reservations.

The anti-tumour effect of heat was first reported by Busch in 1866, when he noted the disappearance of a sarcoma following erysipelas accompanied by high fever. Local hyperthermia is now used in the treatment of various malignancies and other diseases. Innovative ways of generating heat include electromagnetic transmission and ultrasound (Sterzer, 1979; Mendecki *et al.*, 1980). The rationale behind the development of microwave hyperthermia is the assumption that hyperplastic cellular elements in benign prostatic hypertrophy will react to local prostatic heating in much the same way that neoplastic tissue does. This has resulted in the development of the Prostathermer System (Biodan Medical Systems Ltd, Rehovot, Israel), a device which emits local deep microwave hyperthermia with a maximum temperature of 42.5 ± 1°C. Since it became available some 3 years ago, several reports have been published which recommend its use in the treatment of BPH (Yerushalmi *et al.*, 1985; Leib *et al.*, 1986; Servadio *et al.*, 1986, 1987, 1988; Lindner *et al.*, 1987). These series were small and difficult to interpret because they included various prostatic diseases.

We have been treating BPH patients with this device for 2 years and now present our findings.

Patients and Methods

The study group consisted of 114 patients with BPH. In all cases the enlarged prostates had been confirmed both digitally and ultrasonographically. Most patients were considered poor surgical risks because of other diseases and the remainder were men who for subjective reasons wished to avoid or postpone surgery. None was on alpha-blocker treatment. Some had failed to respond to pharmacological treatment or had been obliged to discontinue it because of side effects. Excluded were patients with urinary infection, previous prostatectomy, known urethral strictures, neurogenic bladder, prostatic carcinoma, cystolithiasis, pre-

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vious rectal surgery, rectal wall thickness exceeding 10 mm and prostate height (antero-posterior) over 55 mm.

A total of 83 patients aged between 67 and 91 years (average 81) had obstructive symptoms (symptom score $\leqslant 12$) and objective evidence of outflow obstruction. None had evidence of urinary infection at the time of treatment. A group of 31 patients with indwelling catheters, aged from 70 to 87 years (average 77), was also studied. The catheters had been inserted to relieve acute urinary retention and had been in place for periods ranging from 1 to 13 months. In each case at least 1 attempt had been made to withdraw the catheter but all had proved unsuccessful.

Each patient was assessed twice before treatment and once during treatment. Follow-up was carried out 1 week after treatment and then at intervals of 1, 3, 6 and 12 months. At each visit both subjective and objective data were recorded and urine culture was performed. Subjective parameters included scoring for obstructive symptoms: quality of urinary stream and intermittency (Table 1). Symptom scores were elicited on each visit by the same investigator (R.S.) in order to assess changes in bladder outlet obstruction. The scoring system was adapted from the Madsen and Iversen (1983) symptom scale. Total score ranged from 2 to 8. Response to treatment was considered significant only after the symptom score had increased by more than 2 points. Information was also collected on irritative symptoms: frequency, urgency and nocturia. Objective parameters included transrectal ultrasonography with maximal volume calculations, measurement of residual volume and peak urinary flow.

Transrectal and transabdominal ultrasonography measurements (Kretz-Technik, Combision 320, Austria) were obtained in order to derive the volume calculation. The total prostatic volume was estimated by the following formula:

$$(\text{length} \times \text{width} \times \text{height} \times 0.524) = \text{Volume}$$

Table 1 Subjective (Obstructive) Scoring System

	Parameter	
Score	*Intermittency*	*Stream*
4	<20% of attempts	Normal
3	20–50%	Decreased but trajectory
2	>50%	Decreased size and force
1	Always	Only with great effort

Highest score 8; lowest score 2.

A decrease of more than 20% of the pre-treatment values was considered an anatomo-morphological response to treatment.

Residual urine was measured by catheter drainage and uroflowmetry; in several patients urethral pressure profiles were performed using the LectroMed (U.K.) Multichannel Urodynamic Unit. An objective scoring system was devised which took into account both the maximal flow rate at given urine volumes and multiplied it with a score given for residual volumes measured (Table 2).

The Prostathermer, model 99-D, has already been described in detail (Yerushalmi *et al.*, 1985; Leib *et al.*, 1986; Servadio *et al.*, 1986, 1987). It includes a 915MHz 100 W microwave generator, a specially designed rectal probe, a cooling device for the rectal wall and special thermo-couples for monitoring rectal and prostatic urethral temperatures. The latter were measured via a transducer introduced through a specially designed 18F Foley catheter. The maximal prostatic temperature was calculated continuously throughout treatment and its estimation was based on the temperature

Table 2 Objective Parameters

A Urinary Flow Rate (UFR)

	Total volume				
Peak flow rate (ml/s)	*0–50*	*51–100*	*101–150*	*151–200*	*>201*
>20	9	9	9	9	9
18–19.9	9	9	9	8.5	8
16–17.9	9	9	8.5	8	7.5
14–15.9	9	8.5	8	7.5	7
12–13.9	8.5	8	7.5	7	6.5
10–11.9	7.5	7	6.5	6	5.5
8–9.9	6.5	6	5.5	5	4.5
6–7.9	5.5	5	4.5	4	3.5
4–5.0	4.5	4	3.5	3	2.5
0–3.9	3.5	3	2.5	2	1.5

B Residual Urinary Volume (RUV) Scoring Table

Volume (ml)	*Points*
0–50	5
51–100	4
101–150	3
151–200	2
>201	1

C Objective Measure Score

UFR score × RUV score

depicted in the rectum and prostatic urethra. An IBM PC-XT type computer was used for constant accurate control of the apparatus and for the collection of data.

All treatment was administered on an out-patient basis and all patients signed a consent form. Neither anaesthesia nor sedation was used and treatment was carried out with the patients seated comfortably in a semilithotomy position, after the rectal probe and Foley catheter were introduced and maintained in a constant position. Patients were discharged as soon as the treatment session ended and were instructed not to take any medication (*e.g.* alpha-blockers) that might interfere with urination. Each session lasted 60 min and was repeated once or twice weekly. Each patient without a catheter received 4 to 7 sessions on a weekly basis. Patients with an indwelling catheter received 8 to 10 sessions twice-weekly. The maximal temperature in the prostatic urethra was maintained at 42.5 ± 1°C. A maximum of about 40 W was used.

No antibiotics were used routinely for prophylaxis. Only in cases where infection was present before treatment (16 of 31 cases with indwelling catheters) was an antibiotic prescribed for the whole treatment period.

Results

Eighty-three patients with severe obstructive symptoms commenced treatment. Six withdrew for personal reasons and treatment was discontinued in 1 case because of high fever and urinary infection. Four patients had an acute myocardial infarction during treatment; 2 had prior ischaemic heart disease and three died. Treatment was discontinued in the fourth case. One patient developed gross haematuria which neccessitated immediate prostatectomy. Thus 71 patients completed therapy. Four died of other concomitant diseases during the follow-up period.

Symptoms

The initial mean (±SD) score was 4.6 ± 1.4 (range 2–7). One week after treatment the score increased to 5.5 ± 1.5 and was maintained at all 4 follow-up visits (5.5, 5.9, 6.0, 5.9 respectively). The pre- and post-treatment values were compared and the increase was found to be highly significant (*t* test $P<0.001$). No differences were noted between any of the subjective scores during the 12 months' follow-up period. Only 37 patients had a higher score after treatment and a significant improvement (by more than 2 points) was noted in only 18 cases (25%). The remainder had either unchanged or decreased scores.

Prostate size

Prostate size and volume were recorded at the pre-treatment visit and at the 1-month follow-up after completion of treatment. The mean (±SD) prostatic volume at the starting point was 41.00 ± 21.38 ml and at the 1-month follow-up was 39.62 ± 17.14. The decrease was not statistically significant (*t* test $P=0.71$). In only 13% of cases was a decrease of more than 20% noted. An increase of more than 20% was noted in 14% of cases.

Objective parameters

The mean pre-treatment peak flow rate (ml/s) was 10.2 ± 5.3 and the post-treatment values at 1 week and 1, 3 and 6 months were 11.2 ± 5.3, 11.9 ± 5.4, 12.7 ± 5.6, 12.1 ± 5.8 respectively. The increase in the mean peak flow rate was not statistically significant. Seventeen patients had pre-treatment peak flow values exceeding 15 ml/s. The change in residual urine as a result of treatment was more pronounced and therefore statistically highly significant ($P<0.01$). Pre-treatment mean residual urine volume (ml) was 130 ± 93 compared with 63 ± 52, 61 ± 51, 62 ± 50, 42 ± 30 and 56 ± 46 at 1 week, 1, 3, 6 and 12 months' follow-up. It is clear that after the initial decrease in residual volume it remained fairly constant. As a result of the change in the 2 objective measurements, the calculated pre-treatment mean scoring (Table 2) was 21.22 ± 9.70 and an immediate increase to 28.24 ± 10.63 was noted 1 week after treatment. This was highly significant ($P<0.001$) and was maintained steadily during the follow-up period (28.86 at 1 month, 28.28 at 3 months, 29.24 at 6 months and 27.80 at 12 months). Only 30 patients (32%) had an increase in score of at least 20%.

Overall improvement

When considering men with improvement in both objective and subjective parameters, 20 (28%) were considered successful; 38 were "total failures" according to both criteria and another 13 (18%) benefited in only 1 of the 2 categories.

Indwelling catheter group

Thirty-one patients began therapy in this group. Two did not complete treatment (1 died and the other discontinued treatment for unknown reasons). Thus 29 patients were available for assessment. In only 2 cases did clinical urinary infection develop during treatment and this was successfully treated with intravenous antibiotics. Nineteen patients (65%) dispensed with their catheters. Three were lost to follow-up after successful catheter extraction. Sixteen patients were seen at the 1-month follow-up, all without a catheter and doing well. Although they did not attend for further follow-up, we understand that after 12 months they remain catheter-free. Eight patients were seen at the 6- and 12-month follow-up visits, all doing well without a catheter. Ten patients (35%) were unable to dispense with their indwelling catheters, even for a short period of time.

Discussion

Despite the excellent results obtained by surgery in most patients with BPH, it is hoped that a satisfactory method of non-surgical treatment may be found and the search for an effective drug or treatment occupies the attention of many research workers. This alternative would best serve elderly patients with frequent coincidental cardiac, renal or pulmonary pathology which greatly increase the risks involved in surgery. With this in mind, Leib *et al.* (1986) began their experiments on the canine prostate and later published their preliminary experience in treating men with BPH and other prostatic pathology with microwave local hyperthermia (Servadio *et al.*, 1986). In a small but unknown number of patients with urinary retention caused by BPH, they demonstrated only minimal response and no change in the size of the prostate gland. Promising subjective results led them to continue their studies and 3 further contributions have since been made: 2 by the same group (Servadio *et al.*, 1987, 1988) and 1 from another centre (Lindner *et al.*, 1987). Servadio *et al.* (1987), in their largest detailed series, described 29 patients with BPH, several of them with indwelling catheters. Eight patients were included as controls and received no treatment. Allocation to treatment, however, was not randomised and the study was neither double-blind nor placebo-controlled. The authors were favourably impressed by the outcome, namely a mean 16% decrease in prostatic cross-sectional area and the possibility of removing the indwelling catheter in 8 of 13 patients. They also noted a subjective improvement in irritative symptoms and nocturia.

A 70% improvement in objective symptoms and 90% in subjective symptoms was reported by the same research group (Servadio *et al.*, 1988) in a heterogeneous group of patients with BPH and chronic prostatitis.

Lindner *et al.* (1987) reported their experience in 6 patients with indwelling catheters. Five no longer needed catheters and at 6-month follow-up after termination of therapy were still doing well according to objective and subjective criteria.

Any attempt to evaluate therapy in BPH must take into account 3 points:

(1) Spontaneous fluctuations in the clinical course of BPH, as first recorded by Clark (1937).
(2) The importance of selecting objective parameters which measure changes in urethral obstruction due solely to the effect of treatment on the prostate. Castro *et al.* (1969) found that the maximum flow rate best correlated with the cross-sectional diameters of the urethra, the latter being the ultimate expression of prostatic obstruction producing clinical BPH.
(3) The dramatic placebo effect observed in both subjective and objective variables measured in many BPH studies. Up to 60% of the improvement was reported to be due to the placebo effect (Clark, 1937; Resnick *et al.*, 1983).

In the present series, the need to insert a transurethral 18 F catheter on each treatment session further complicated results and might be regarded as dilatation treatment in its own right. In fact, this is still used (recently with revived interest and enthusiasm) as a treatment for BPH (Castaneda *et al.*, 1987).

With these points in mind, our results and those previously reported should be regarded with caution. Although we have presented the largest homogeneous group of 114 elderly males with BPH only, treated with local hyperthermia, this is still only a preliminary study. No major complications were noted during and after treatment, except for haematuria in 4 patients. Despite repeated catheterisation during treatment in patients with high residual volumes, no urinary infection was encountered. The results from this non-randomised open study fall short of results obtained by mere placebo treatment in other studies. An overall subjective improvement in obstructive symptoms in less than 50% of patients and a significant improvement in only 25% contrasts with the 90% seen by others (Servadio *et al.*, 1988). The objective parameters yield even less promising results, since no change in prostatic size was demonstrated, in contrast to the findings by Servadio *et al.* (1988), and only minor changes were detected in the peak flow rates.

The 83% success rate in removing a permanent indwelling catheter reported by Lindner *et al.* (1987) should take into consideration the small number of patients (6) and the 61% success rate in removing indwelling catheters in our larger series should be reviewed in the light of criticisms mentioned earlier.

However, the fact that the catheter-free period extended to over 12 months in the successful cases is important and can hardly be attributed either to the effect of dilatation or to a placebo effect alone. The statistically significant and consistent changes observed in patients without indwelling catheters, contrasted with the small number of patients benefiting from these positive changes, may indicate that only a subgroup of patients may benefit from this treatment. Such a group has not yet been defined and recommending this mode of treatment indiscriminately seems unwise at present.

In the meantime while awaiting the results of randomised protocols as suggested by Linder *et al.* (1987) and ourselves, results based on histopathological changes provide evidence in support of this treatment. In the 4 cases where the prostate was removed by open prostatectomy after treatment failure, no histological changes were seen when using the light microscope.

Studies of prostate cancer patients treated by the same modality and identical protocol have been carried out by Stormaier *et al.* (1988). It was concluded that definite signs of cell destruction could not be observed and that the shrinkage of prostatic tumours alleged earlier could not be explained by histopathologically proven cell destruction.

Despite the fairly large number of patients in the present series (and because of the study design), we consider our results to be preliminary and we recommend that randomised long-term studies be completed before conclusions are drawn about this new treatment for BPH.

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Balloon Dilatation of the Prostate: Technique and Early Results

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Summary—Fourteen men with outflow obstruction were treated by balloon dilatation of the prostatic urethra using 25 and 30 mm balloon catheters. Significant improvement in objective measurement of outflow obstruction was noted in only 2 patients.

Balloon dilatation of the prostatic urethra has been reported to be an effective method of treating outflow obstruction (Burhenne *et al.*, 1984; Castenada *et al.*, 1987). Patients with predominantly "middle" lobe enlargement are reported to be unsuitable for balloon dilatation because the balloon has the effect of pushing the lobe into the bladder and it can thus return to its original position and act as a ball valve. The majority of patients, however, are suitable for treatment. We have investigated the efficacy of balloon dilatation of the prostate in 14 men with outflow obstruction.

Patients and Methods

Fourteen patients with outflow obstruction were assessed by clinical examination and estimation of serum acid phosphatatase and prostate specific antigen (PSA). Free flow rates were obtained on 2 separate occasions and a cystometrogram was performed pre-operatively. Each patient had a transrectal ultrasound examination of the prostate with estimation of prostatic volume using serial planimetric measurements.

Thirteen patients (age range 43–78 years) had benign prostatic hypertrophy and 1 had a T3 carcinoma of the prostate. One patient had undergone transurethral resection of the prostate 6 years previously.

Two sizes of balloon catheter (Meditech™) were used: 25 and 30 mm. The balloon catheter has a central channel to allow its passage over a guide wire. At either end of the balloon there is a metal ring for radiological identification, which can also be easily visualised with an endoscope. At the distal end of the catheter there is a plastic ring which allows traction to be applied to the balloon during the procedure. In 7 patients the balloon was sited radiologically and in 7 it was sited endoscopically under direct vision. Radiological placement of the balloon catheters was done under sedoanalgesia (pethidine 1 mg/kg and midazolam 0·05–0·1 mg/kg). Patients having endoscopic placement of the balloon catheter had a general anaesthetic. The procedure was covered by a single dose of preoperative gentamycin.

Endoscopic technique

A floppy tipped guide wire was passed into the bladder following endoscopic examination of the prostate and bladder. A 14 F endoscope was then passed beside the catheter and the verumontanum identified. The metal ring of the balloon catheter was placed at the verumontanum and the balloon was inflated by an assistant while the operator ensured that the balloon was maintained in the correct position. The balloon was inflated with approximately 40 ml of water using a 50 ml syringe. When inflated to maximum, a 10 ml syringe of water was injected into the balloon until firm pressure did not allow the balloon to fill further.

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This provided approximately 10 atmospheres of pressure within the balloon. The balloon was inflated for 10 min and then removed. The patient was catheterised without any need for irrigation.

Radiological technique

Xylocaine gel 2% was instilled into the urethra and the patient was given intravenous sedation. A retrograde urethrogram was first performed with the patient in an oblique position and the position of the external sphincter was noted relative to the landmarks of the bony pelvis. It was important to maintain the patient's position during the procedure. A guide wire was advanced into the bladder and a balloon catheter passed over this, which was then inflated with dilute contrast. The distal marker of the balloon was placed at the distal sphincter as judged by the relative bony landmarks. Check urethrography was performed using a small catheter placed in the urethra alongside the balloon catheter and the use of a penile clamp helped to distend the bulbar urethra during the procedure (Fig. 1).

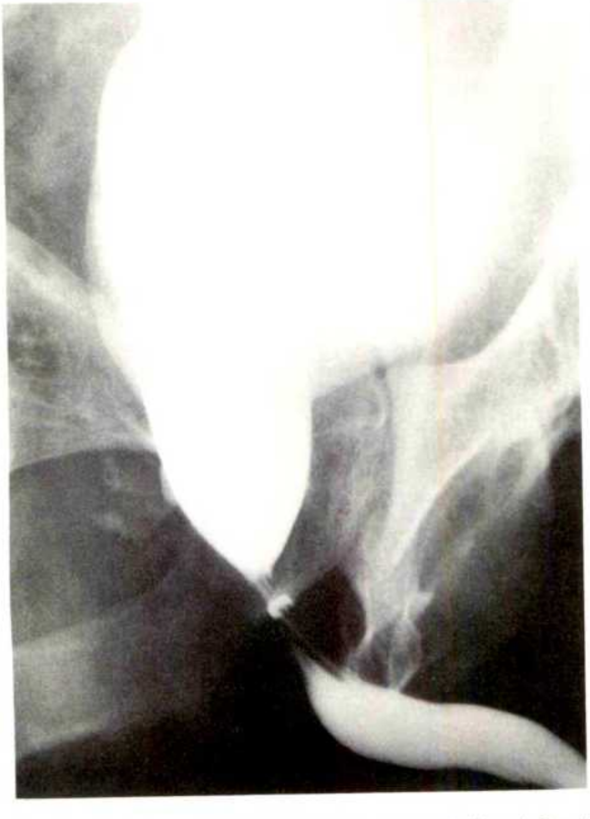

Fig. 1 Intraoperative urethrogram showing the balloon inflated proximal to the external sphincter.

Patients were seen 3 months after the procedure and free flow rates were obtained as well as an ultrasound examination of residual urine.

Results

All patients developed bladder spasms with symptoms of urgency and pain after the procedure and 2 required opiate analgesia within the first 24 h. The mean hospital stay was 3·5 days but this could be reduced if the geographical location of the hospital was more convenient for day case surgery. No patient developed post-operative urinary tract infection or retrograde ejaculation. The results of the pre- and post-operative flow studies are shown in Figure 2. Two of the 13 patients in the benign group had a satisfactory result and achieved significant improvement in free flow rates. One of these patients had a previous transurethral resection of the prostate. The patient with carcinoma of the prostate experienced significant relief of symptoms of hesitancy and nocturia (from 5 to 1 per night) and his flow rate increased from 3 to 7 ml/s. There was no significant change in flow characteristics or residual volumes in any of the remaining patients. Nine patients reported some symptomatic improvement; 5 requested further treatment and 3 have had transurethral resection of the prostate with satisfactory results.

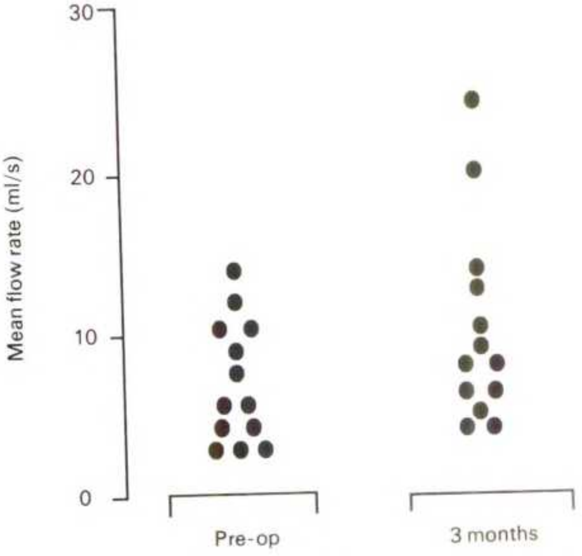

Fig. 2 Comparison of mean flow rates pre- and post-operatively.

Discussion

The potential advantages of using balloon dilatation for patients with benign prostatic hypertrophy are that the procedure can be performed without general anaesthesia or blood transfusion and minimal hospitalisation is required. Also, because the bladder neck is not ablated there is less risk of developing retrograde ejaculation following the procedure.

In animal experiments, balloon dilatation of the prostate has produced intraprostatic haemorrhages but no other serious side effects (Quinn *et al.*, 1985; Castenada *et al.*, 1987). The present study confirms that the procedure is safe; there were no complications and no sexually active patient developed retrograde ejaculation. Although Castenada *et al.*, (1987) and Burhenne *et al.* (1984) described symptomatic improvement, they did not report objective results. Castenada (1988) noted that 21 of 23 patients with "lateral lobe" hypertrophy had significant or complete resolution of symptoms, while only 5 of 12 patients with "middle lobe" hypertrophy had resolution of symptoms. In our study 50% of patients had symptomatic relief of symptoms and only 15% had objective improvement in flowmetry. Thus no firm conclusions can be drawn from the studies presented to date.

The results of the present study indicate that in the majority of patients, balloon dilatation of the prostate does not improve objective measurements of outflow obstruction, using either a 25 or 30 mm balloon. These findings are supported by other British workers. Larger balloons (35 mm) are now becoming available and may be more effective. During the procedure, particularly when performed under radiological screening, there may be some difficulty in maintaining the position of the balloon catheter. As the balloon is inflated the catheter can clearly be felt to be drawn into the bladder and considerable (sometimes alarming) traction has to be applied to keep the balloon in position. The use of a small Foley catheter to screen the position of the catheter was particularly useful and the catheter had to be repositioned several times in both the endoscopic and the radiological group. We were satisfied in all cases that the catheter was finally positioned correctly and feel that malpositioning was an unlikely cause of the results presented. A more plausible explanation is that the benign prostate is quite compliant and can easily accomodate the degree of stretch afforded by this size of balloon catheter, reverting to its normal configuration shortly after the procedure.

Urologists who are considering using balloon dilatation should consider using catheters larger than 30 mm.

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Video Transurethral Resection

Report of 200 Cases

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Summary—Two hundred transurethral resections of the prostate (TURPs) were performed using a controlled continuous flow (CCF) resectoscope attached to a video camera by direct-beam coupler. Standing comfortably, the surgeon used a video monitor as the source of judgment for manipulating the loop. Data obtained were statistically similar to those obtained from 400 previous resections using the same resectoscope by the conventional viewing method. TURP can be performed safely, more efficiently and more comfortably with the CCF video technique.

Although video endoscopy is being used increasingly by orthopaedic surgeons and gastroenterologists, acceptance of the technique among urologists has been slow. This is largely because traditional irrigation systems do not provide the control of flow and bladder distension needed for a clear image on the video monitor.

Videoprostatectomy was introduced in the United Kingdom by O'Boyle *et al.* (1984), who found that the technique was surprisingly easy to learn and offered many advantages to the surgeon. The video technique has subsequently been used by urologists in the United States (Widran, 1987b, 1988), Japan (Tazaki and Tachibana, 1989; Tajima *et al.*, 1984), and Israel (Yachia, 1987).

Basic equipment for videoprostatectomy includes a high quality resectoscope, light source, microvideo camera, video controller system and monitor. A direct-beam coupler is preferred for attaching the resectoscope lens to the camera. A split-beam coupler gives the surgeon the option of either looking through the resectoscope or viewing the monitor, but darkens the field and unduly unbalances the resectoscope. A videocassette recorder is a useful option for documentation and teaching.

The resection procedure itself is essentially unchanged, but a brief learning period is necessary to adapt to the video equipment. The surgeon must view the monitor instead of looking through the resectoscope. For proper orientation, the camera must remain at the 12 o'clock position relative to the surgeon's body, regardless of the rotation of the endoscope. The non-dominant hand holds the camera steady while the dominant hand operates the resectoscope. The weight of the camera changes the balance of the resectoscope. During cutting, the surgeon must appreciate that depth perception is altered on the video image and magnification makes the pieces of resected tissue appear larger than they are. Unless the resectoscope lens and camera coupler are dry before they are connected, the video picture may become cloudy due to condensation. If this happens, surgery must be interrupted temporarily while the coupler is disconnected and the coupler lens and resectoscope lens are dried. Blood absorbs light, darkening the view on the monitor. Bleeding vessels must be fulgurated promptly. If several vessels bleed simultaneously and cause complete "red outs" on the monitor, flow rates can be increased by turning the console dial.

Most surgeons adapt quickly to these changes. If necessary, during the early learning period, the camera can be easily disconnected to allow use of the conventional lens.

This report describes the technique and results of videoprostatectomy as performed with the controlled continuous flow resectoscope in 200

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patients. This study is an extension of a previous report of 50 patients (Widran, 1988). Data from this broader series, with a total of 200 patients operated on by video TURP, indicate that differences between conventional TURP and video TURP are minimal; the only statistically significant difference is that patients with video TURP were discharged from hospital an average of 3 days earlier. The earlier release of these patients probably resulted from cost-containment measures rather than from any outcome of the procedure itself.

Patients and Methods

A series of 200 consecutive patients underwent surgery for prostatic obstruction in 2 Chicago hospitals between January 1987 and December 1988; 153 had benign prostatic hypertrophy (BPH) and 47 had carcinoma of the prostate. They ranged in age from 51 to 91 years. All operations were performed by the author.

Equipment included a 26 F or 28 F Controlled Continuous Flow Resectoscope (Wid-Med, Inc., Chicago), developed by the author (Widran, 1983, 1984, 1985, 1987a), equipped with a Mega-View 30° lens. The CCF resectoscope is the only instrument that allows the surgeon to control fluid inflow and outflow and to monitor and control intravesical pressure. The resectoscope loop is powered by a solid-state electrosurgical device and light is provided by a high-intensity 300 W halogen light source with a flexible 4.5 mm diameter fibreoptic cable. The resectoscope lens is attached by direct-beam coupler to a 4¾-ounce, high-resolution camera with a CCD image sensor. A remote signal-receiving unit connects the camera to a 20-inch high-resolution television monitor.

The endoscope is connected to the CCF pumping console by inflow and outflow tubing and by an extension cable attached to the pressure transducer. An Abbott flow reservoir bag linked to two 1.5% glycine irrigating solution bags provides uninterrupted delivery of fluid to the infusion pump. Fluid flow rates are adjustable by rheostat control up to 1000 ml/min. The pumping console is under the electronic control of an intravesical pressure sensor in the resectoscope.

The pressure sensor shuts off the inflow pump and activates a buzzer if intravesical pressure reaches adjustable preset limits. These limits are based on the bladder's capacity and reaction to filling under anaesthesia, as measured by the cystometrogram; 50 cm of water is the usual upper limit of pressure allowed.

This study followed the standard TURP procedure developed by the author (Widran, 1987a). White balance is adjusted at the start of the video procedure by placing the resectoscope lens over a white gauze sponge for several seconds while the nurse depresses the white balance button on the remote video unit. Adjustment of colour contrast is automatic.

Bladder capacity under anaesthesia is measured as soon as the resectoscope is placed in the bladder. The index finger is used to shut off the outflow valve (Fig. 1) until the bladder is sufficiently distended. As the bladder fills and the far wall of the bladder recedes, the surgeon opens the outflow valve and resection begins. Compliance allows the bladder to remain distended as pressure is maintained as close as possible to 10 cm H_2O. Pressure is not allowed to exceed 50 cm H_2O. When shut-off pressure is reached, the surgeon unblocks the outflow holes (Fig. 2) by advancing the instrument into the bladder (Widran 1987a).

While standing or sitting comfortably, the surgeon uses the video monitor as the source of judgment for manipulating the loop to cut tissue and fulgurate arterial bleeders. To provide the best view, the resectoscope lens is kept close to the tissue. After each cut the resectoscope is pushed back into the bladder to unblock the outflow holes and minimise elevations in intravesical pressure.

Bleeding vessels are easily located by placing the lens on the tissue and temporarily increasing flow rates, then moving the resectoscope behind the bleeding area. The outflow valve can be temporarily shut off to increase the flow away from the lens.

The CCF resectoscope need not be disconnected until the end of the procedure, when the Ellik evacuator is used to remove tissue. The video magnification is very helpful for locating tissue remnants.

Central venous pressure is measured peri-operatively and serum sodium is measured post-operatively.

Results

As Tables 1 and 2 indicate, data from the present study are similar to those from an earlier study of 400 patients who underwent conventional TURP with the CCF resectoscope (Widran, 1988). The earlier group consisted of 359 patients with BPH and 41 with carcinoma of the prostate. The patients, aged 49 to 94 years, underwent surgery between 1984 and 1986. The only statistically significant difference in the results for the 2 groups was the

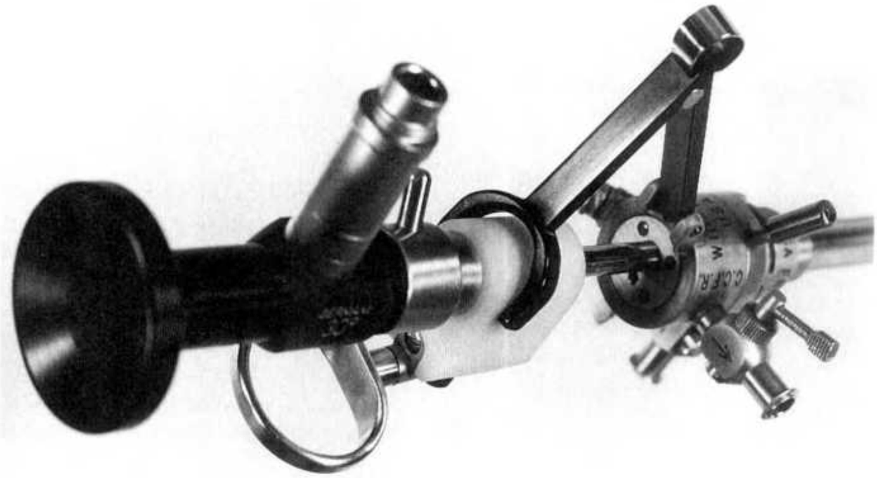

Fig. 1 Outflow valve on resectoscope. Index finger is used to control bladder distension.

mean post-operative length of hospitalisation. The shorter stay for the video group (5.4 versus 8.02 days) may be related to cost-containment measures rather than to differences in the surgical procedure. Less tissue was resected per minute of surgery with the video method than with the conventional method (0.79 versus 0.83 g), but the difference was not statistically significant. The range with the video method was 0.6 to 1.8 g/min.

Blood loss was estimated by the Platt (1979) formula for converting haemoglobin and haematocrit differences to ml of blood loss:

1 haematocrit point = 0.34 g Hb/100 ml blood.

This method of measuring blood loss is associated with inaccuracies related to the conversion formula and to haematocrit differences before and after surgery. From a practical standpoint, blood loss

Table 1 Data and Results

Data	*Group 1* (mean ± SD)*	*Group 2†*
Age of patients (years)	70.1 ± 6.3	72.3 ± 9.8
Weight of tissue removed (g)	36.20 ± 28.76	34.34 ± 17.34
Length of surgery (min)	43.19 ± 16.70	43.37 ± 15.66
Volume of irrigating fluid used (ml)	19,444 ± 9,080	19,627 ± 7,990
Bladder capacity under anaesthesia (ml)	374 ± 165	394 ± 78
Haemoglobin decrease after surgery (g/l)	1.31 ± 2.42	1.25 ± 1.17
Haematocrit decrease after surgery	0.038 ± 0.058	0.032 ± 0.057
Number of blood transfusions	7	2
Estimated blood loss (Platt formula)	9.53 ± 1.36 ml/g of resected tissue 7.50 ± 2.81 ml/min of surgery	9.35 ± 1.26 ml/g of resected tissue 7.40 ± 1.63 ml/min of surgery
Length of post-operative hospital stay (days)	8.02 ± 4.45	5.4 ± 3.07

* 400 TURPs with conventional method using CCF.

† 200 TURPs with video method using CCF.

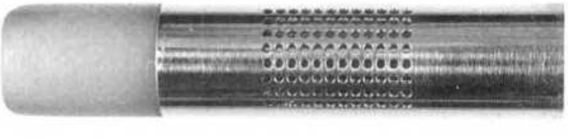

Fig. 2 Outflow holes on sheath of CCF resectoscope. Advancing the resectoscope into the bladder unblocks the holes and allows intravesical pressure to drop.

Table 2 Measurements Related to Fluid Absorption

Parameter	*Group 1**	*Group 2†*
Sodium decrease after surgery (mean ± SD)	4.05 ± 3.90 mmol/l	1.89 ± 2.23 mmol/l
Sodium depletion below 130 mEq/l (% of patients)	11.5	0
Patients monitored for central venous pressure (% of total group)	79.0	26.0
Central venous pressure elevation above 20 cm of water (% of patients monitored)	12.0	0

* 400 TURPs with conventional method using CCF.
† 200 TURPs with video method using CCF.

figures reported here are well within the accepted safety range discussed by others using similar resectoscopes and other flow systems.

As postulated by Widran (1988), comparison of the data from the 400 patients who had traditional TURP, the first 50 video patients, and the next 150 video patients (total 200) reveals that several data have become closer to equivalence now that the video group has become larger. For example, estimated mean blood loss (ml/g of resected tissue) was 9.53, 8.72 and 9.35 respectively; estimated mean blood loss (ml/min of resection) was 7.50, 5.73 and 7.40; weight of tissue removed (g) was 36.20, 30.43 and 34.34; length of surgery (min) was 43.19, 46.27 and 43.37; volume of irrigating fluid used (ml) was 19,222, 20,880 and 19,627; and haematocrit decrease after surgery was 0.038, 0.027 and 0.032.

Table 2 lists measurements related to fluid absorption. Because anaesthetists are increasingly reluctant to perform routine measurements of central venous pressure (CVP) only 26% of patients in the current study were monitored compared with 79% in the earlier study. Non-invasive monitoring of central venous pressure is under consideration for future studies.

Discussion

Video TURP using the CCF resectoscope system offers many advantages. The surgeon can stand or sit in a comfortable position and so minimise fatigue. The entire surgical team participates in the procedure, greatly facilitating teaching and patient care (Appleton *et al.*, 1984). With a clear visual field and up to 50 × magnification on a 20″ monitor, small bleeding vessels often missed in conventional TURP are easy to see and fulgurate. "Red-outs" are minimised and easily controlled. There is no need to interrupt surgery for teaching purposes or to empty the patient's bladder.

The CCF system monitors and controls intravesical pressure non-invasively and limits absorption during TURP. This may reduce the risk of overhydration and electrolyte disturbances, which can result in the potentially fatal TUR syndrome (Henderson and Middleton, 1980; Logie *et al.*, 1980). It has been shown that lowering intravesical pressure by only 10 cm H_2O (from 70 cm to 60 cm H_2O) can reduce total absorption by almost half (Madsen and Naber, 1973).

In an earlier study, absorption during TURP was decreased by modifying the CCF technique (Widran, 1987a). In the first 200 procedures performed with the CCF system, sodium levels fell below 130 mEq/l in 14% of patients. Advancing the resectoscope into the bladder after each cut keeps the pressure low and minimises absorption. Sodium levels did not fall below 130 mEq/l in any of the patients in the current study.

A more sophisticated way to measure blood loss is being sought for future studies. Also needed is a non-invasive technique to monitor CVP, perhaps using thoracic impedance (Casthely *et al.*, 1981) or Doppler equipment, so that monitoring can be included in the routine protocol for TURPs. It is important to determine the significance of intravesical pressure and morbidity and to define a safe pressure range during surgery. These steps would provide important new safety benefits for TURP patients.

Video TURP with the CCF system offers unique advantages for the urologist and can provide important safety benefits for patients. For many orthopaedic surgeons and other specialists, video procedures have become a standard tool for performing endoscopic surgery. The time has now come for urologists to join their ranks in adopting this important new technology.

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Experience with Ultrasound Guided Transperineal Prostatic Needle Biopsy 1985–1988

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Summary—A consecutive series of 143 ultrasound guided biopsies of the prostate have been analysed. In 84 patients, in whom carcinoma was suspected by both digital examination and ultrasound, 49 cancers were confirmed histologically. In 29 patients in whom digital examination suggested cancer but ultrasound was normal, 2 cancers were confirmed. In 20 patients with a normal digital examination but a suspicious ultrasound appearance, no cancers were proven.

Cancer of the prostate is one of the commonest malignancies in men in the United Kingdom, with 9524 new cases registered in England and Wales in 1984 (Office of Population Censuses and Surveys, 1988). Unfortunately, 80% of these patients present with advanced and therefore incurable disease (Veterans Administration Cooperative Urological Group, 1967). Transrectal ultrasound (TRUS) offers an objective, safe and easily reproducible method of imaging the prostate gland and provides the most reliable technique for imaging early prostate cancer, since clinical examination, computed tomography and magnetic resonance imaging cannot reliably identify small tumours (Denkaus *et al.*, 1983; Poon *et al.*, 1985).

TRUS examinations can be easily performed using a hand-held transducer with the patient in the left lateral decubitus position. Scans of the prostate can be performed in both the axial and sagittal planes. Small lesions suspected of malignancy can be localised accurately by ultrasound so that a biopsy needle can be placed within the lesion to obtain a specimen for diagnostic examination. We report our experience in performing a consecutive series of transperineal needle biopsies using transrectal ultrasound guidance, and discuss potential future developments for prostatic biopsy.

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Patients and Methods

All patients were initially assessed by digital rectal examination (DRE) and TRUS. The transrectal ultrasound scans were performed in the left lateral decubitus position using a Bruel and Kjaer 1846 Scanner and a 4MHz radial transducer. All scans were reported by a consultant radiologist (GJG/RC). Biopsies were performed on patients with an abnormality indicative of malignancy found on DRE and/or TRUS.

A further 10 patients in whom a diagnosis of prostate cancer had been previously established were also biopsied. General anaesthesia was used in 28 patients and the remaining 114 were biopsied under local anaesthesia (1% lignocaine) with intravenous diazepam as a sedative.

Biopsies were performed by a standard technique as described by Holm and Gammelgaard (1981). With the patient in the lithotomy position, the transducer is inserted into the rectum and the prostate is visualised. The perineum is cleaned with antiseptic (Betadine) and the region draped with sterile towels. The multichannel biopsy guide attachment is fixed to a transducer. Following infiltration of the perineal skin with local anaesthetic, the biopsy needle is inserted through one of the channels of the biopsy guide into the perineum and advanced until the needle tip is visualised on the scan monitor (Fig. 1). Cytological samples were

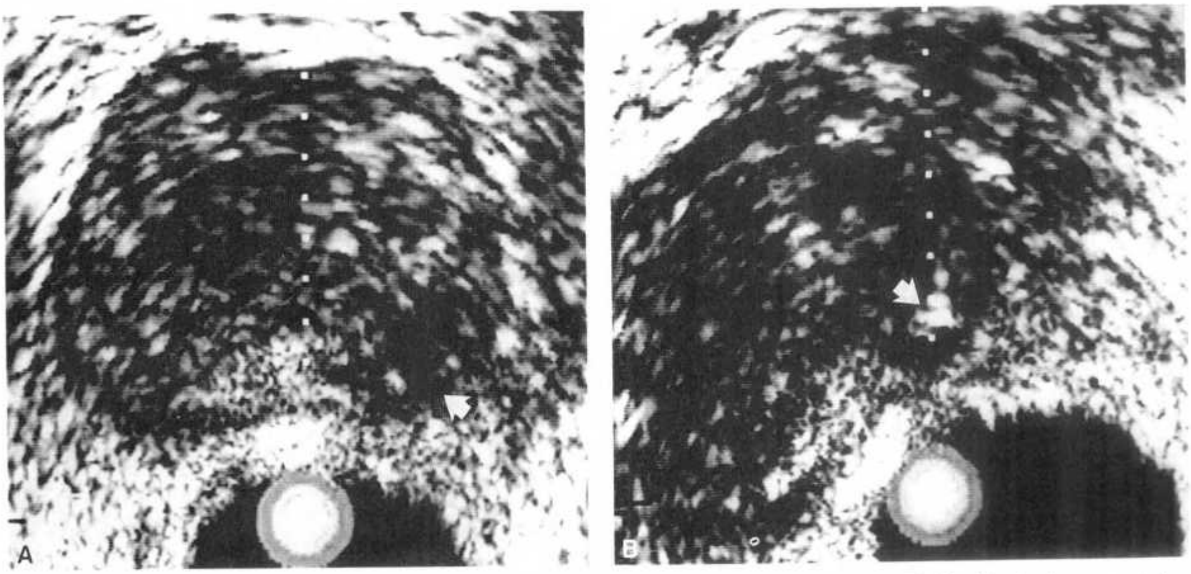

Fig. 1 (A) Axial scan of prostate in the hypoechoic area (arrow) in the left posterior quadrant. (B) Needle tip demonstrated as echogenic focus (arrow) within region to be biopsied.

taken from the abnormal area with a 22 gauge needle, initally a spinal needle but later a "Westcott" biopsy needle, and specimens for histological examination were obtained with a 14 gauge "Trucut" needle.

Results

A total of 157 patients (mean age 72 years) were biopsied using transrectal ultrasound guidance between October 1985 and October 1988. Clinical notes and ultrasound films were available on 145 of these patients but the final number available for study was 143, since 2 biopsies were abandoned for technical reasons. The patients were divided into 4 groups:

Group i. Patients with an abnormality indicative of malignancy (firm or hard gland or nodule) on DRE but benign appearances on ultrasound scan (n = 29).
Group ii. Patients with an abnormality indicative of malignancy on both DRE and TRUS (n = 84).
Group iii. Patients with a benign gland on DRE but a suspicious gland on TRUS (n = 20).
Group iv. Patients with histologically proven malignancy, *e.g.* those with TO tumours and those treated by radiotherapy in whom a change of therapy was being considered (n = 10).

The histological results in Groups i to iii are demonstrated in Table 1. Table 2 shows the results for biopsies performed since March 1987.

Initially, cytological and histological specimens were obtained in all cases. There was, however, a problem in obtaining adequate specimens for cytological diagnosis. A comparative study of cytology and histology is currently under way, but it was unusual to find that the cytological specimen contributed any more information than

Table 1 Histological Results October 1985–October 1988

	No. of patients	*Results*		
		Malignant	*Prostatitis*	*Benign/normal*
Group i	29	2	2	25
Group ii	84	49	3	32
Group iii	20	0	0	20
Total	133	51	5	77

Table 2 Histological Results March 1987–October 1988

	No. of patients	*Results*		
		Malignant	*Prostatitis*	*Benign/normal*
Group i	4	1	0	3
Group ii	37	23	2	12
Group iii	10	0	0	10
Total	51	24	2	25

that obtained histologically. In the most recent patients, a sample for cytological analysis has not been taken and diagnosis has been made solely from the histological specimen.

No patient whose biopsy was performed under local anaesthesia developed urinary retention and there were no significant infective complications. In cases where the biopsy was done under general anaesthesia, cystourethroscopy was performed concurrently; 3 patients in this group had a significant exacerbation in outflow symptoms, 2 requiring catheterisation. Three patients had infective complications, including 2 of the 3 with exacerbated outflow symptoms. One patient had fresh clot in his bladder which was washed out during cystoscopy without further complication. Another patient's biopsy showed granulomatous prostatitis and 7 months later he presented again with a lump in his perineum, presumably in the biopsy tract. This was excised and showed marked inflammation and reactive changes including fibrosis, fat necrosis and foreign body giant cell response, possibly to some foreign material introduced at the time of biopsy.

There were 3 cases of haematospermia following biopsy. Biopsies on 3 of 5 patients who had been treated by ^{125}I implantation were followed by bleeding from the needle puncture site for 1 to 2 h. There were no instances of macroscopic haematuria apart from the initial post-biopsy specimen of urine.

Discussion

During the 3-year study period approximately 3600 scans were performed on about 2200 patients; of these 157 were referred for biopsy and 23 with histologically proven cancer were treated by transperineal implantation of ^{125}I seeds under ultrasound guidance.

Considerable advances have been made during this period in the technique of ultrasound scanning of the prostate and in our understanding of the ultrasound appearance of prostate cancer. In the technical field there have been major developments. Initially, transrectal scanners used radial transducers to produce axial images of the prostate, but from the mid 1980s transducers have been available which can produce sagittal images. Axial images are important for assessing the overall symmetry of the gland and the integrity of the gland capsule, and are necessary for performing volumetric measurements. Sagittal images are advantageous in assessing the bladder neck region and are more useful for performing ultrasound guided biopsies because they enable the whole length of the biopsy needle within the prostate to be visualised. Subsequent technical developments have seen the introduction of biplanar probes which allow visualisation of the prostate in both axial and sagittal planes without changing the transducer. Most of these biplanar transducers have the disadvantage that the transducers for the axial and sagittal images are separated along the probe and correlation of an abnormal area in the 2 planes is achieved only by movement of the probe. In 1989 a truly multiplanar transducer became available (Bruel & Kjaer 8551 transducer) which produces a sector scan that can be rotated into any plane. This is a major advance in prostatic ultrasonography; using a 7MHz frequency, it produces high definition images of the internal prostatic anatomy and can be used for prostatic biopsy by both the transrectal and transperineal routes.

In addition to these technical developments, our understanding of the ultrasonic appearance of the prostate has improved, particularly the appearance of prostate cancer. It was originally thought that prostate cancers were mainly echogenic (Harada *et al.*, 1980) but it is now widely accepted that most are echo-poor (Lee *et al.*, 1985; Griffiths *et al.*, 1987). We have found that 6% of proven confined cancers may be isoechoic, although Dähnert *et al.* (1986) identified 24% of cancers as isoechoic. Confusion about the ultrasound appearance of cancer was probably caused by problems in establishing precisely which echo pattern represented the area of malignant change. Most authors were able to recognise a heterogeneous gland with suspicious features of malignancy, but many ultrasonologists then incorrectly considered that the relative echogenicity of the normal area of the gland represented the area of prostatic cancer. This is why our group initially described cancer as echogenic (Brooman *et al.*, 1981). It was only when the ultrasound guided biopsy service commenced that we realised that the area of cancer was normally echo-poor.

A nodule felt during rectal examination of the prostate may represent an early confined cancer, but Jewett (1956) showed that at least 50% of prostatic nodules were benign. It may be impossible to distinguish digitally between a benign and a malignant nodule and transperineal needle biopsy of prostatic nodules has an error rate of approximately 30% (Kaufmann and Schultz, 1962). It was hoped that ultrasonically guided needle biopsy would improve the accuracy of diagnosis of prostatic nodules, although a report by Resnick (1988) comparing ultrasound guided biopsy with digitally directed biopsy felt that the former may not be necessary as a routine procedure when a distinct nodule is palpable. Histological results in the present series reveal that of the 84 patients in whom both digital examination and ultrasound suggested malignancy, 49 cancers were proven (58%). Of those patients in whom palpation suggested possible malignancy but ultrasound was normal, only 2 cancers were found; in patients in whom ultrasound suggested possible malignancy but palpation was normal, no cancers were proven.

During the early part of this series we believed that many cancers were echogenic. Experience with ultrasound guided biopsy led to a major reinterpretation. Figure 2 illustrates the heterogeneous appearance of a malignant prostate. The gland was reported as malignant and a biopsy of the echogenic area in the right lobe was taken. The sample was reported as benign on histological examination, but when a subsequent sample was taken from the echo-poor area in the left lobe, the diagnosis of prostate cancer was confirmed.

Most authors now agree that most prostate cancers appear echo-poor. However, not all echo-poor areas are cancers and some ultrasonic appearances which we considered potentially malignant in the earlier part of this series we would now report as benign. For instance, 3 echo-poor lesions at the base of the prostate were regarded as possibly malignant in 1985 and 1986. We would now regard these as cysts in the region of the ejaculatory ducts. Such cystic structures in this region are relatively common but were a cause of misinterpretation during the earlier part of the series.

Our scanning protocols have also changed during the study period. The initial diagnostic scans are usually performed by a specially trained radiographer and the films are reported by a radiologist. There may be problems in interpreting the film if the prostate is not fully within the focal zone of the transducer and in the earlier part of the study this sometimes gave an impression of echo-poor prostatic lesions. It is now standard practice to record all initial diagnostic examinations on videotape as well as on film and to ensure that any suspicious echo pattern within the prostate is within the focal zone of the transducer. Suspicious appearances are now rescanned by a radiologist before a recommendation is made for biopsy. In deciding whether to perform a biopsy, close correlation between the findings on digital examination and ultrasound is necessary. Our results suggest that biopsy may not be indicated if the prostate feels normal in the region of the ultrasonic abnormality, since no cancer was diagnosed in patients in whom the ultrasound scan was abnormal but the prostate was digitally normal.

The scans in this series were performed with a 4MHz frequency transducer and most authors now advocate the use of 7MHz frequency for ultrasonic evaluation of the prostate. The increased resolution provided by this higher frequency gives better

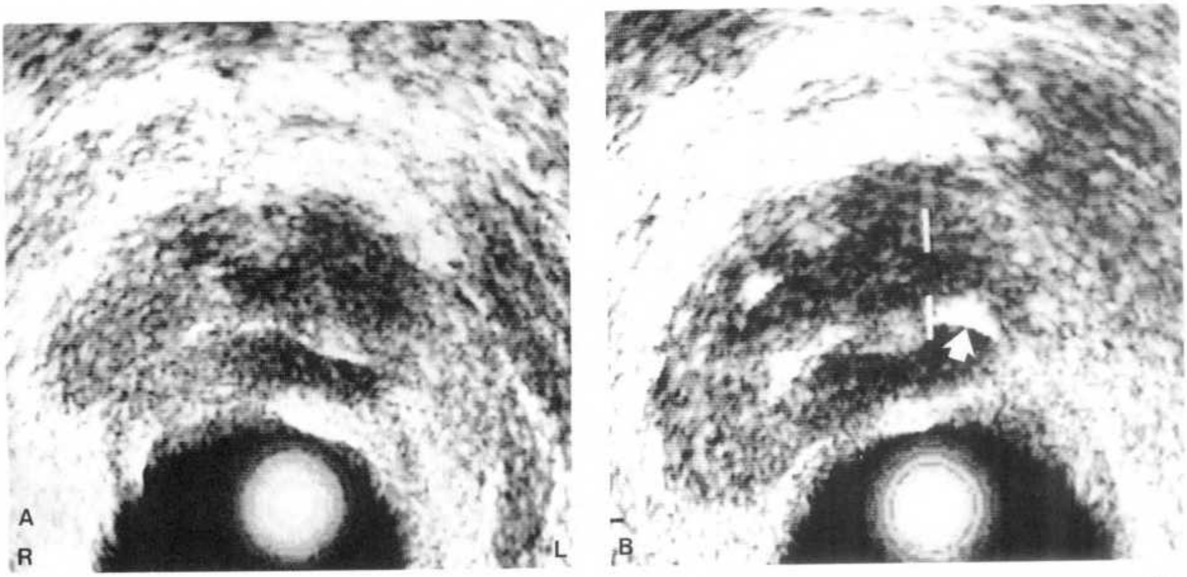

Fig. 2 (A) Axial scan of malignant prostate. The right lobe is echogenic, the left lobe echo-poor. (B) Needle tip (arrow) within echo-poor left lobe. Histological examination of sample demonstrated adenocarcinoma.

delineation of prostatic anatomy and pathology and demonstrates cancers ultrasonically at a stage when they are not digitally palpable. An analysis of 256 hypoechoic lesions of the prostate found by TRUS using a 7MHz transducer was presented by Lee *et al.* (1989). These patients were evaluated by DRE, prostate specific antigen (PSA) and ultrasound guided biopsy of the hypoechoic area. The positive predictive value for TRUS alone was 41%; this increased to 61% if the patient had a palpable abnormality on DRE, 52% if the PSA levels were abnormal and 71% if both the DRE results and PSA levels were abnormal. No cancers were detected in hypoechoic lesions measuring 1 cm or less if both DRE results and PSA levels were normal. The results reported by Lee *et al.* (1989) reinforce the view that correlation of digital examination, transrectal ultrasound measurements and serum PSA levels is necessary to assess the prostate for potential malignancy.

Lee *et al.* (1989) obtained their ultrasound guided biopsies via a transrectal rather than a transperineal route. There has been considerable interest recently in the use of the transrectal route for ultrasound guided prostate biopsy. This has been made possible by the use of an end firing sector or multi-planar transducer. Torp-Pedersen *et al.* (1989) performed 149 biopsies via this route without serious complications. They reported 7 cases of haematospermia following the procedure and 2 of pyrexia. In view of the latter, they now perform the biopsy under prophylatic antibiotic cover.

The transrectal route offers several technical advantages over the transperineal route for performing prostate biopsy under ultrasound guidance and may well become the preferred method. The path of the biopsy needle is much shorter and deviation of the needle within the prostate is less likely to occur, which makes positioning easier. The procedure is quicker, since there is no skin preparation, and local anaesthesia is not required. It is also better tolerated by the patient.

Some of the biopsies in this series were performed in patients who had been treated by either external radiotherapy to the prostate or ^{125}I seed implantation. In these cases it was more difficult to advance and localise the needle tip precisely because the texture of the gland was much harder than normal. The echogenic focus of the seeds was also sometimes difficult to distinguish from the echogenic focus of the needle tip (Fig. 3).

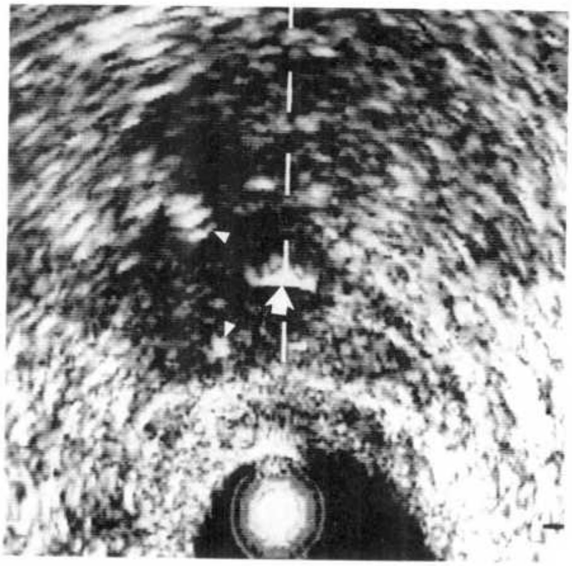

Fig. 3 Axial scan in patient treated by ^{125}I seed implantation. The seeds (arrowheads) are difficult to distinguish from the needle tip (arrow).

We believe that palpation and ultrasound are complementary and that close correlation between the findings of palpation, ultrasound and serum PSA measurements is necessary to evaluate the prostate fully and to decide which patients need biopsy.

Transrectal ultrasound provides the most detailed demonstration of internal prostate anatomy currently available and offers the greatest potential for precise biopsy of the prostate. The technique may be adapted for other purposes, including aspiration of a prostatic abscess. An ejaculatory duct cyst was aspirated by this technique in our unit; 4 ml of fluid were obtained, with resolution of the cyst. Needle placement within the seminal vesicles is also possible, *e.g.* to biopsy that area in the staging of prostatic cancer, to obtain bacteriological specimens or to aspirate the seminal vesicles for infertility investigations. Biopsy of a pelvic mass which recurred following salvage cytoprostatectomy for post-radiotherapy recurrent transitional cell carcinoma was also possible by a modification of the biopsy technique.

Ultrasound guided biopsy with a 4MHz axial transducer has improved the accuracy of detection of prostatic cancer. Future developments with higher frequency multiplanar transducers should make prostatic biopsy a faster and better tolerated technique and improve the accuracy of cancer detection within the prostate.

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Histological Grading of Prostatic Carcinoma in Prostatectomy Specimens

Comparison of Prognostic Accuracy of Five Grading Systems

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Summary—The prognostic accuracy of 5 histological grading systems (Broders, Anderson, Mostofi, Gleason and Mostofi-Schroeder) was compared. Grading was performed on 50 prostatectomy specimens by 5 pathologists. The results were averaged so as to reduce the impact of inter-observer variation. The Cox proportional hazards model was used to estimate the relationship between average grading scores and both time-to-recurrence and time-to-death by prostatic carcinoma. Age at surgery was considered to be a possible confounding factor and adjusted accordingly. The prognostic impact of the 5 grading systems (related to both recurrence and death caused by prostatic carcinoma) was judged by the likelihood ratio (LR) test score (χ^2 distributed with 1 df); for time-to-recurrence for the Mostofi-Schroeder score the LR was 6.54 and for the Gleason system it was 1.79. A stepwise procedure demonstrated that the best prognostic performance was reached with the Mostofi-Schroeder and Broders systems used together (with Mostofi-Schroeder weighted 1.5 times larger than Broders). For time-to-recurrence the median grading result was also used, giving results similar to the mean grading result. For time-to-death from prostatic carcinoma the LR test scores for all grading systems were relatively low. In this analysis the outcome of the Gleason system showed a minimum of prognostic ability, whereas the Broders and Mostofi-Schroeder systems had a reasonable predictive ability. Since the inter-observer variation of the Mostofi-Schroeder system was large, the Broders system is preferable. The restrictions and implications of this study are discussed and a brief review of the prognostic importance of grading of prostatic carcinoma is presented.

Carcinoma of the prostate is a common malignancy whose incidence demonstrates a geographically and demographically related distribution ranging from 0.84 for Shanghai to 100.20 for the black population in Alameda County, California per 100,000 male population (Wynder *et al.*, 1971; Ross *et al.*, 1983; Catalona, 1984; Zaridze *et al.*, 1984). The reason for these variations in incidence and prevalence remains unknown. Since latent or incidental carcinomas have been omitted (Dhom, 1983; Yamabe *et al.*, 1986), the true figures on incidence and prevalence are often underestimated. The mortality rate of disseminated prostatic tumours shows similar variations, ranging from 2.51 (Japan) to 29.1 (St Vincent and Grenadines) per 100,000 male population (Wynder *et al.*, 1971; Ross *et al.*, 1983; Catalona, 1984; Zaridze *et al.*, 1984). The large difference between incidence and mortality rate reflects the wide variation in clinical behaviour of prostatic carcinoma. At initial diagnosis it may present as a harmless incidental carcinoma or as an extended tumour with a tendency to metastasise, leading to death. Almost 97% of prostatic tumours show histopathological acinar structures and are therefore designated adenocarcinomas (Utz and Farrow, 1969).

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Pathologists have sought histological, cytological, immunological and morphometric parameters in an attempt to predict biological agressiveness and several histological grading systems have been developed to forecast the biological behaviour of the carcinomas (Mostofi, 1976; Murphy and Whitmore, 1979; Grayhack and Assimos, 1983).

The large number of grading systems described in the literature is indicative of the controversy concerning the most reliable system and large inter- and intra-observer variations have been demonstrated (Ten Kate *et al.*, 1986). We have correlated the original data with the clinical follow-up of patients incorporated in this survey and present our findings.

Patients and Methods

From the original series of Belt and Schroeder of 464 patients who underwent total perineal prostatectomy for localised prostatic carcinoma (Whitmore, 1956), 50 patients were randomly selected (Belt and Schroeder, 1972; Schroeder and Belt, 1975). In this group the average age at the time of surgery was 66 years (range 48–83). The mean period of follow-up was 125 months (range 8–317). The survival curves for time-to-death and time-to-first recurrence in these 50 patients did not differ from the curves of a much larger random selection in the series of Belt and Schroeder, whose original series was used to devise a new grading method described by Schroeder *et al.* (1985a, b, c).

We were able to obtain follow-up details for all 50 patients. At the end of the follow-up period 11 patients were still alive without progression. For analysis of time-to-first recurrence (19 patients), 31 patients were considered "censored" and for time-to-death by prostatic carcinoma (16 patients), 34 were considered "censored" (Fig.). None of the patients who showed progression is still alive. This series is one of the few with a mean follow-up period of more than 10 years. Recurrence after prostatectomy occurred in 19 patients. The time interval until first recurrence varied from 8 to 133 months (mean 51). Treatment modalities for these recurrences differed and were in accordance with protocols at that time. All patients with a tumour which showed progression died at time intervals ranging from 1 to 164 months (mean 45). After excluding 3 patients who died from other causes, time-to-death in the recurrence group ranged from 1 to 164 months (average 33).

Prostatectomy specimens were routinely fixed in 4% formaldehyde solution. Section was performed in a stepwise fashion and each specimen was submitted to complete histological examination. Slides were routinely stained with Mayer's haematoxylin and eosin. The number of slides available for microscopic survey per prostatectomy specimen ranged from 2 to 11. The number of slides in which tumour was present varied from 1 to 9 (mean 3).

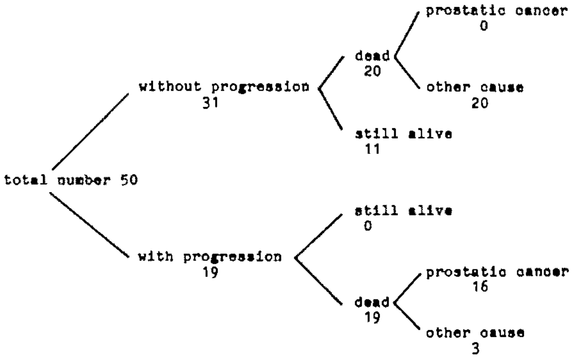

Fig. Follow-up of the study group (50 patients).

Grading systems

The 50 cases were evaluated by 5 pathologists using the general grading system of Broders, the Anderson (hospital) system, the Mostofi system, the system described by Gleason and the Mostofi-Schroeder system (Broders, 1926; Gleason, 1966; Mellinger *et al.*, 1967; Mostofi, 1975; Brawn *et al.*, 1982; Schroeder *et al.*, 1985a, b, c). The Gleason system was used as originally described since, by definition, a crude linear transformation realised by rearrangement of Gleason scores in 3 main groups will not increase the prognostic impact of this system (Babaian and Grunow, 1985).

The percentage distribution of grading scores for each system is listed in Table 1 (Ten Kate *et al.*, 1986).

Statistical analysis

Statistical analysis was performed using the Cox proportional hazards model (Cox, 1972, 1975). The following events ("endpoints") were considered:

Progression ($N = 19$)

and irrespective of the occurrence of progression:

Death caused by prostatic carcinoma ($N = 16$).

The BMDP programme 2L was used (Dixon, 1983). The likelihood ratio (LR) test score was used for judging and comparing the predictive ability of each of the 5 systems. The contribution of an

Table 1 Percentage of Tumours Attributed to the Various Grades of the Broders, Anderson, Mostofi, Gleason and Mostofi-Schroeder Grading Systems Assigned by all Pathologists

Grades	*Broders (%)*	*Anderson (%)*	*Mostofi (%)*	*Gleason (%)*	*Mostofi-Schroeder (%)*
1	58	41	9	—	2
2	25	43	48	0	14
3	12	10	43	2	36
4	5	6	—	10	34
5	—	—	—	18	14
6	—	—	—	47	—
7	—	—	—	11	—
8	—	—	—	8	—
9	—	—	—	2	—
10	—	—	—	2	—

explanatory variable to the likelihood function is supposed to represent its predictive ability (Green and Symons, 1983). This contribution is quantified by means of the likelihood ratio test score which has an asymptotical chi-square distribution with 1 degree of freedom. The contribution is significant (at the 5% level) if the LR test score exceeds the value 3.84. The 5 scores (from the 5 pathologists) for each grading system were summarised into 1 interval-scaled explanatory variable by taking the average score. For the endpoint of progression, the median score was also considered and compared with the average score. For each grading system a separate analysis was done, with age at surgery included as a confounding variable. For the endpoint of progression a stepwise analysis was also performed, starting from a model including all 5 grading systems followed by stepwise elimination of insignificant grading methods. The purpose of this latter analysis was to investigate if 2 (or more) grading systems used simultaneously provide better prognostic information than one single system.

Results

Cox proportional hazard model and LR test scores for progression of prostatic carcinoma

Patients' age (at time of surgery) and the average (respectively, the median) grading score were chosen as explanatory variables. The average (median) grading score was calculated for each patient and for each grading system as the arithmetic mean (as the median) of the scores of the 5 pathologists; 19 of 50 patients developed progression (Fig.). Time-to-progression was computed after date of surgery as zero-point. Progression was defined as local recurrence or metastastic disease irrespective of a possible lethal course. The estimated coefficients of the proportional hazard function and LR test scores are summarised in Table 2. Estimated coefficients for the average grading scores varied from 1.497 (Mostofi) to 0.327 (Gleason) and represent the estimated proportional increase in risk of progression to an increase of one score in the grading system applied. LR test scores ranged from 6.54 (Mostofi-Schroeder) to 1.79 (Gleason). Since the latter values are used for judging prognostic performance, our results indicate that both the Mostofi-Schroeder and the Broders systems have the highest prognostic capability. The Gleason system reveals the poorest prognostic power.

An identical ordering in prognostic accuracy was obtained when median grading scores were used instead of the mean values (results not tabulated).

The results of the stepwise procedure are presented in Table 3. It appeared that the Mostofi-Schroeder and the Broders systems (both mean and median values) remained together in the model at the final step along with the forced presence of age at surgery. This result indicates that these 2 grading

Table 2 Estimated Proportional Hazards Model for Progression (of Prostatic Carcinoma) and Results of chi-square Likelihood Ratio (LR) Test per Grading System (Single Regression Analysis)

	Coefficient	*SE*	*LR test score*
Mostofi–Schroeder			
average grading score over pathologists	1.145	0.474	6.54
age	0.058	0.031	
Broders			
average grading score over pathologists	0.822	0.309	6.32
age	0.038	0.032	
Anderson			
average grading score over pathologists	0.839	0.383	4.44
age	0.034	0.033	
Mostofi			
average grading score over pathologists	1.497	0.741	4.36
age	0.030	0.034	
Gleason			
average grading score over pathologists	0.327	0.240	1.79
age	0.054	0.032	

SE = standard error.

Table 3 Final Results of Stepwise Analysis for Progression of Prostatic Cancer. Coefficients of Cox Proportional Hazards Model and chi-square Likelihood Ratio (LR) Test Scores

	Coefficient	*SE*	*LR test score*
Age	0.040	0.032	
Broders (median)	0.637	0.275	4.81
Mostofi–Schroeder (median)	1.157	0.400	9.19
Age	0.041	0.032	
Broders (average)	0.649	0.318	3.82
Mostofi–Schroeder (average)	0.943	0.486	4.05

SE = standard error.

systems reflect different dimensions of grading prostatic carcinoma. From the estimated coefficients in Table 3 it can be concluded that a weighted average of the Broders system and the Mostofi-Schroeder method might be the best prognostic index for progression (with the Mostofi-Schroeder system weighted 1.5 times larger than the Broders method).

Cox proportional hazard model and LR test scores for death from prostatic carcinoma

Explanatory variables chosen for this statistical analysis were identical to those described in the previous section. The endpoint considered here was time-to-death caused by prostatic carcinoma. From a total of 50 patients, 16 died from the sequelae of disseminated prostatic carcinoma (Fig.). The estimated coefficients of the hazard function ranged from 0.999 (Mostofi) to 0.189 (Gleason). However, for all of the grading systems the prognostic performance for death from prostatic carcinoma as reflected by the LR test score was poor and varied from 2.17 (Mostofi-Schroeder) to 0.59 (Gleason). Results of this analysis are shown in Table 4. Because of the similar results with the mean and median scores obtained for the end-point progression, only the mean score was analysed here.

Individual prognostic accuracy (including data of Mostofi) for progression of prostatic carcinoma

For both the Mostofi and the Mostofi-Schroeder systems the scores assigned to the slides by Mostofi himself were available. The individual prognostic accuracy for progression of prostatic carcinoma of 6 pathologists (Mostofi and pathologists A–E) was calculated for the Mostofi and Mostofi-Schroeder grading systems (Table 5). Again, the LR test was used to judge prognostic performance.

Table 4 Estimated Proportional Hazards Model for Death (Caused by Prostatic Carcinoma) and Results of chi-square Likelihood Ratio (LR) Test per Grading System

	Coefficient	*SE*	*LR test score*
Broders			
average grading score over pathologists	0.436	0.294	2.01
age	0.051	0.036	
Anderson			
average grading score over pathologists	0.557	0.380	1.99
age	0.048	0.036	
Mostofi			
average grading score over pathologists	0.999	0.767	1.75
age	0.044	0.038	
Gleason			
average grading score over pathologists	0.189	0.245	0.59
age	0.061	0.035	
Mostofi–Schroeder			
average grading score over pathologists	0.672	0.465	2.17
age	0.059	0.034	

SE = standard error.

In both grading systems a large inter-observer variation was found (Table 5). With regard to the Mostofi-Schroeder system, 3 pathologists revealed statistical significance (Mostofi, pathologist A and pathologist B). LR test scores varied from 9.18 (pathologist B) to 0.18 (pathologist C). Using the Mostofi system, statistical significance was found only for the grading data of Mostofi himself and pathologist B. The prognostic performance reflected by the LR test scores ranged from 6.26 (Mostofi) to 0.13 (pathologist D).

Discussion

In the present study the prognostic performance of 5 current grading systems has been compared. Since a long period of follow-up after surgery was available for all patients, it was even possible to use time-to-death as a response.

To enable comparison of the prognostic accuracy of the grading systems, the impact of inter-observer variation on the various grading systems was reduced by averaging the grading scores assigned by the 5 pathologists. This might be debatable since a grading score is considered to be an ordinally-scaled covariate. Therefore, in the statistical analysis for progression of prostatic cancer the median

Table 5 Estimated Proportional Hazards Model for Progression and Results of chi-square Likelihood Ratio (LR) Test for 2 Grading Systems (Mostofi and Mostofi–Schroeder) and 6 Pathologists (including Mostofi)

	Coefficient	*SE*	*LR test score*
Mostofi–Schroeder			
grading scores of Mostofi	0.668	0.310	4.89
age	0.087	0.034	
grading scores of pathologist A	0.700	0.302	5.31
age	0.064	0.033	
grading scores of pathologist B	0.847	0.288	9.18
age	0.057	0.030	
grading scores of pathologist C	0.107	0.257	0.18
age	0.064	0.030	
grading scores of pathologist D	0.395	0.316	1.58
age	0.052	0.031	
grading scores of pathologist E	0.333	0.233	1.90
age	0.058	0.030	
Mostofi			
grading scores of Mostofi	1.147	0.456	6.26
age	0.066	0.031	
grading scores of pathologist A	0.396	0.427	0.91
age	0.052	0.033	
grading scores of pathologist B	0.924	0.457	4.37
age	0.049	0.030	
grading scores of pathologist C	0.607	0.477	1.76
age	0.054	0.032	
grading scores of pathologist D	0.219	0.617	0.13
age	0.060	0.033	
grading scores of pathologist E	0.564	0.379	2.26
age	0.053	0.030	

SE = standard error.

grading values (measured by 5 pathologists) were also used. The dependence of the responses (recurrence or death from prostatic carcinoma) on these average (and median) grading scores was estimated by the Cox proportional hazards model, while correcting for age at surgery. This model allows one to relate multiplicatively the instantaneous risk of "failure" (namely progression or death from prostatic carcinoma) to a set of candidate covariates. Moreover, a stepwise analysis including initially 6 candidate covariates (age and 5 grading methods) was performed to study the influence upon the prognostic performance of using 2 or more grading systems simultaneously. The antilog of the estimated coefficients represents the multiplicative increase in risk of progression or death related to 1 unit increase in the explanatory factor.

The chi-square likelihood ratio test score was used for judging and mutually comparing the prognostic performance of the grading systems.

The inter-observer variation in assignment of grading scores to prostatic carcinomas in 50 patients was described by Ten Kate *et al.* (1986). As (dis)agreement score the κ-value for each grading system was measured, but in none of the grading systems was a high degree of consensus ($\kappa > 0.70$) attained as judged from the κ values. However, the agreement among pathologists using the Broders and Anderson systems was considered fair to reasonable (κ ranging from 0.40 to 0.70). The remaining grading systems showed poor agreement amongst participating pathologists ($\kappa < 0.40$).

When the results presented in Tables 2 and 4 are compared, it becomes evident that histological grading can more accurately predict the event of progression (Table 2) than the event of death by prostatic carcinoma (Table 4). This discrepancy could be partly attributed to the follow-up data of a single patient who showed progression 46 months after surgery, but survived for the extremely long period of 164 months before eventually dying of the sequelae of disseminated prostatic carcinoma. Thus we decided to use time-to-progression (Tables 2 and 3) for comparison of the prognostic performance of the different histological grading systems. From Cox regression it appeared that all but 1 of the systems were statistically significant, the Gleason system being the exception (LR test score 1.79). The prognostic performance for the event of progression (Table 2) of the grading systems of Broders and Mostofi-Schroeder was superior to that of the other systems. The use of median instead of average values did not result in a different ranking of grading systems as regards their prognostic accuracy with respect to progression.

For the risk of death by prostatic carcinoma (Table 4), none of the grading systems reached statistical significance. Nevertheless, the trend reflected by the LR test scores for death was similar to that for progression (Table 2).

Stepwise analysis (performed for both average and median values) provided evidence that the Broders and the Mostofi-Schroeder methods, used together, supplied additional prognostic information (Table 3), with the latter method weighted 1.5 times larger than the former. This might be explained by the fact that next to architectural features, exclusively used in the grading performance according to Broders, cyto-nuclear characteristics are also incorporated in the Mostofi-Schroeder system and provide additional prognostic information.

Comparative studies on the prognostic impact of grading systems in prostatic carcinoma applied to the same set of slides are rarely reported. Comparison of these studies with ours is complicated by the use of different statistical techniques and diverse prognostic risk or hazard functions. Mostofi (1976) reviewed grading systems for prostatic carcinoma introduced over a period of half a century (Broders, 1926; Gleason, 1966; Utz and Farrow, 1969). He found that they all promised to give the best prognostic value in the individual course of prostatic carcinoma. Nevertheless, reproducibility of all of these systems is poor.

In an extensive retrospective study in which multivariate analysis was used, Schroeder *et al.* (1985a, b, c) demonstrated that the coexistence of several architectural patterns favoured the prognosis when compared with tumours composed of only 1 prognostically bad histological pattern. In addition, nuclear and mitotic activity should also be considered, since these are important prognosticators in any grading system. Using these 3 parameters (gland formation, mitoses and nuclear anaplasia), 5 different prognostic groups of patients can be identified.

Brawn *et al.* (1982) introduced a new grading system and compared the prognostic accuracy of their system (Anderson) with those described by Mostofi and Gleason in a group of 182 patients with locally advanced carcinoma (stage C) treated by radiotherapy. Follow-up of patients ranged from 3 to 7 years. Grading was performed on transurethral specimens, needle biopsies or both. Survival curves were obtained using the Kaplan-Meier statistical method. Statistical significance of survival curves by histological grades was computed using the Wilcoxon method. Statistical significance was obtained for grade 1 and grade 4 lesions according to the Anderson system.

The Gleason system is probably most often applied and data on its prognostic potential are frequently reported. Cantrell *et al.* (1981) studied the natural course of stage A (incidental) prostatic carcinoma in 117 patients followed up for 2 to 15 years. There was no therapeutic intervention until relapse developed. In 14 patients progression occurred. To gain insight into factors that might predict clinically evident prostatic carcinoma at 4 years and/or predict a crude 4-year survival, a retrospective discriminant analysis using diverse variables was carried out. Grading scores of the Gleason system and extension of tumour at initial diagnosis were the variables discovered to have the highest prognostic value. No patient with a low grade lesion (Gleason score 2–4; $n = 14$) and only 2% of patients with less than 5% tumour volume showed progression. Grading was performed on transurethral currettings or specimens obtained by simple enucleation.

Parfitt *et al.* (1983) studied stage A2 disease (incidentally found extensive carcinomas) and reported that the Gleason grade had some predictive value. Of 16 patients with primary tumours and a Gleason score <4, none appeared to have lymph node metastases on subsequent staging lymphadenectomy.

Kramer *et al.* (1980) also studied the predictive value of Gleason scores of primary tumours for nodal involvement at staging pelvic lymphadenectomy. In their group of 228 patients, irrespective of primary clinical stage, 93% with Gleason sums >7 in initial biopsies showed evidence of lymph node metastases. However, sensitivity in this study was low, since 31% of patients (26/84) with histologically proven lymph node metastases proved to have Gleason sums ranging from 5 to 7. The latter might be attributed to sample error resulting from the use of small tissue samples for grading. When small tissue samples are involved, it is possible that only 1 or 2 minor histological growth patterns are present, whereas a whole specimen would be more representative.

The results presented by Wilson *et al.* (1983) may also be of dubious value due to grading inaccuracies resulting from sample error. They studied prospectively 115 full staged (including pelvic lymphadenectomy) patients with localised prostatic carcinoma (stages A–C). Grading according to a modified Gleason system was carried out on needle biopsies or transurethral specimens. Two of 6 low grade (Gleason sum 2–4) lesions of 16 A2 tumours and 4 of 35 low grade lesions of 53 B1 tumours revealed metastases during follow-up (range 8–71 months). Wilson *et al.* (1983) postulated that low stage, low grade prostatic carcinoma could retain the potential for widespread metastatic disease. Even more interesting is their observation that 9 patients with high grade tumours and without evidence of metastases showed no progression of disease during follow-up

Guinan *et al.* (1983) compared the prognostic ability of 2 grading systems (Gleason and Broders) for the risk of recurrence in 111 patients with clinically localised carcinoma treated by radical surgery. Follow-up ranged from 6 months to 8 years. Statistical significance was computed by means of a chi-square test. Of the 2 systems studied, the Gleason classification system was the less accurate.

The studies reviewed above do not give unequivocal information about which grading system possesses the highest prognostic ability. Although most studies present favourable results for the Gleason system, our data demonstrate a low inter-observer accuracy (Ten Kate *et al.*, 1986) and only limited prognostic ability. The system of Mostofi also exhibits a large inter-observer variation (Ten Kate *et al.*, 1986). Nevertheless, compared with the Gleason system its prognostic accuracy of average (and median) grading scores for the occurrence of progression is relatively high. Our data indicate that the less complicated systems, such as those described by Broders and Brawn (Anderson), reveal not only the highest inter-observer reproducibility (Ten Kate *et al.*, 1986), but also a high prognostic impact. Though inter-observer agreement was low, as reflected in the present study (Table 5), data obtained on the recently introduced system of Mostofi-Schroeder seem promising. The additional prognostic information provided by the use of more than one histological grading system applied to the same tumour is very interesting and further investigations, using larger series and different combinations of grading systems, are indicated.

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Testicular Histology after Treatment with LH-RH Analogue for Carcinoma of the Prostate

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Summary—Orchiectomy was performed in 16 patients because of progression of prostatic cancer despite adequate medical castration with goserelin (Zoladex, ICI) over a mean period of 17.6 months. Severe tubular atrophy was seen in the testes. The Leydig cells also showed signs of atrophy, a fact that may indicate a direct effect of goserelin on these cells. In 1 patient, however, orchiectomy was postponed for 3 months after cessation of medical castration. The serum testosterone had resumed almost normal values and testicular histology revealed intact spermatogenesis and apparently normal Leydig cells.

In Norway, surgical castration has for decades been the treatment of choice for advanced carcinoma of the prostate. In 1984 a Norwegian multi-centre study was initiated which offered such patients chemical castration with a new LH-RH analogue, goserelin. According to the protocol for the study, patients with progression of disease despite the endocrine therapy were subjected to orchiectomy.

The aim of the present investigation was to note the effect of prolonged administration of an LH-RH analogue on testicular histology.

Patients and Methods

Sixteen patients received goserelin 3.6 mg/month subcutaneously for 8 to 26 months (mean 17.6). In spite of this, tumour progression occurred and the patients underwent orchiectomy. Their mean age was 67 years (range 52–77). The testes were immediately fixed in formalin, embedded in paraffin, stained with haematoxylin and eosin and examined under the light microscope. In 1 patient, however, orchiectomy was postponed until 3 months after cessation of 11 months of treatment with the LH-RH analogue.

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Results

Histologically, all testes showed atrophy of the tubular epithelium with loss of spermatogenesis. Only Sertoli cells and some spermatogonia could be seen in the tubular wall. There was considerable peritubular fibrosis (Fig. 1). In some cases, hyalinisation of tubules was seen.

The Leydig cells were small, with pyknotic nuclei and sparse cytoplasm (Fig. 2). Although no quantitative analysis was performed, the number of Leydig cells seemed to be reduced.

The testes from the patient in whom orchiectomy was postponed showed significantly less peritubular fibrosis. Evidence of intact spermatogenesis was found as secondary spermatocytes and spermatids could be seen (Fig. 3). The Leydig cells had pale nuclei with nucleoli usually present. The cytoplasm was abundant, with a rich content of eosinophilic granules (Fig. 4). Starting 1 month after initiation of LH-RH treatment, the serum testosterone in this patient had been below 0.4 nmol/l. Six weeks after cessation of treatment the serum testosterone rose to 0.7 nmol/l, after 9 weeks to 2.5 nmol/l and at 3 months had increased to 9.5 nmol/l (Fig. 5).

Discussion

LH-RH analogues have been introduced as a means

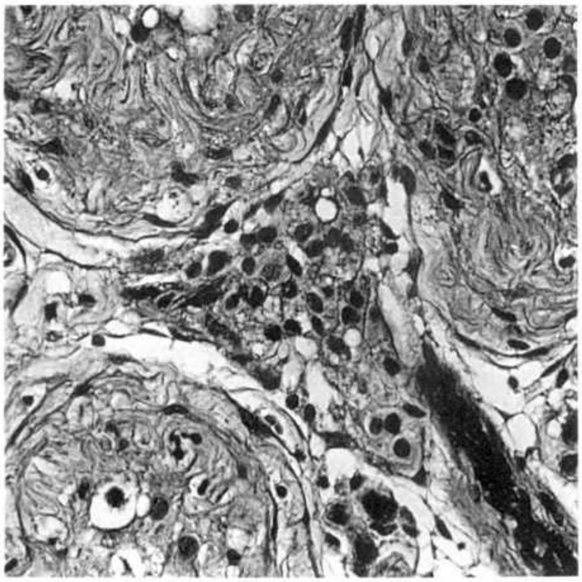

Fig. 1 Low power light micrograph showing tubules with considerable peritubular fibrosis and only Sertoli cells in the tubular wall. (H and E × 300).

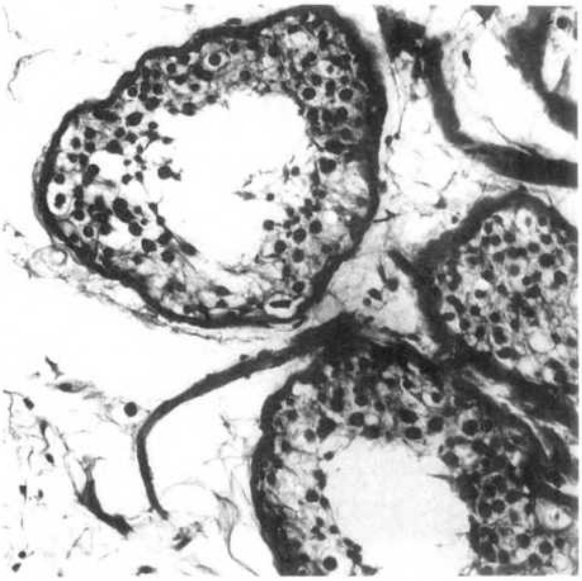

Fig. 3 Low power light micrograph from testis 3 months after cessation of prolonged administration of goserelin. Note the scanty peritubular fibrosis and the thickness of the tubular epithelium, where secondary spermatocytes and spermatids are seen. (H and E × 189).

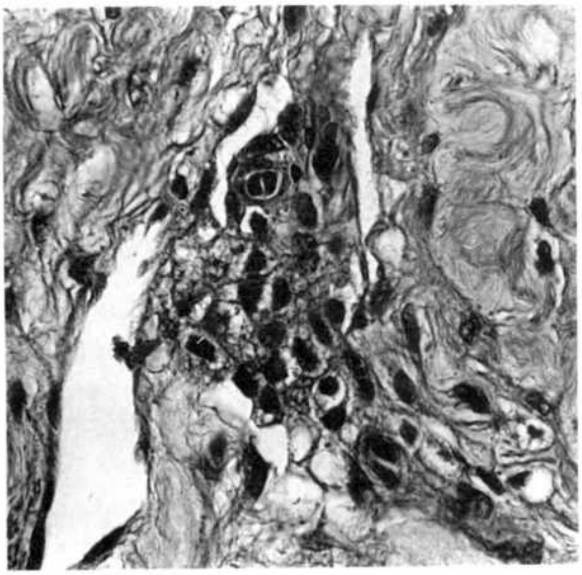

Fig. 2 Closer view of an islet of Leydig cells with pyknotic nuclei and sparse cytoplasm. (H and E × 480).

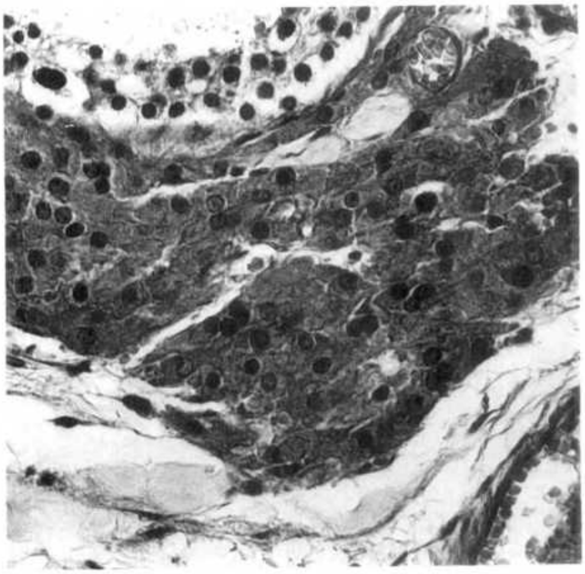

Fig. 4 Closer view of an islet of Leydig cells from the same patient as in Figure 3, showing large cells with abundant cytoplasm containing eosinophilic granules and a pale nucleus with nucleoli present. (H and E × 480).

of reversible, medical castration. It is also an alternative treatment for pubertas praecox. Thus the effect of prolonged administration on testicular histology is of great interest. The general findings of severe tubular atrophy are consistent with the findings by Smith and Urry (1985) in human testes, in rat testes by Labrie *et al.* (1980) and in dog testes by Sandow *et al.* (1980). However, the tubular changes described are also seen in undescended testes after exposure to irradiation, heat, oestrogen

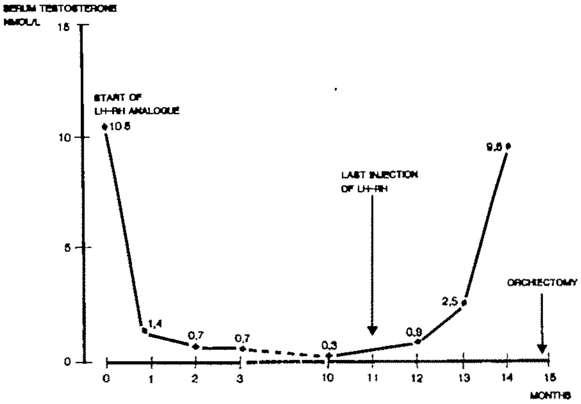

Fig. 5 Development of serum testosterone after cessation of 11 months of treatment with goserelin in a 67-year-old man.

treatment and the administration of several other drugs (Vilar, 1973). Consequently, the tubular findings represent a non-specific testicular reaction to various noxious effects. We agree with Smith and Urry (1985) that in cases of severe peritubular fibrosis the effects on the spermatogenetic epithelium are probably irreversible.

The inhibitory effect of goserelin on spermatogenesis is due to a reduction in the levels of FSH and, more importantly, to a reduction in LH and testosterone. The atrophic changes seen in the Leydig cells may also indicate a direct action of goserelin on human Leydig cells, since no morphological changes have been described in Leydig cells after oestrogen treatment, which is known to depress Leydig cell function through a reduction in the pituitary production of LH and FSH. Elucidation of this difference would require closer ultrastructural and biochemical studies.

Reversibility of the effects of goserelin depends on the ability of the pituitary gland to recommence synthesis of LH and on the ability of Leydig cells to respond to this stimulation. According to the findings in 1 of our patients, both conditions can be fulfilled. It is not known whether the scanty peritubular fibrosis seen in this particular patient means that he reacted to LH-RH treatment with less fibrosis or if much of the fibrosis had disappeared after cessation of treatment. However, since reversal of degenerative histological changes in undescended testes has been reported after orchiopexy (Duvie, 1984), the tubular effects of prolonged LH-RH treatment may also be reversible to some extent.

After prolonged treatment with goserelin, most testes showed significant peritubular fibrosis, severe tubular atrophy and small Leydig cells with pyknotic nuclei. The changes seen in the Leydig cells may reflect a direct action of goserelin.

In 1 patient, however, evidence of intact spermatogenesis and apparently normal Leydig cells were found. Within 3 months serum testosterone had increased to almost normal levels.

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Silver Alloy Coated Catheters Reduce Catheter-associated Bacteriuria

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Summary—The tendency of indwelling catheters to cause urinary tract infection was evaluated in a randomised clinical study of 223 patients. A Foley catheter coated with silver alloy on both inner and outer surfaces was used in 60 patients; 60 others received a Teflonised latex Foley's catheter and the remaining 103 patients were excluded because of antibiotic treatment, diabetes, etc.

There was a statistically significant difference in the incidence of catheter-associated bacteriuria ($> 10^5$ organisms/ml) in the 2 groups after 6 days' catheterisation: 6 patients with the silver coated catheter developed bacteriuria compared with 22 who had the Teflonised latex catheter. This suggests that the silver impregnated urethral catheters reduce the incidence of catheter-associated urinary tract infection.

In recent years the urethral catheter has become essential in the management of many diseases. A significant number of hospitalised patients with an indwelling catheter develop urinary tract infection (Bryan and Reynolds, 1984). Although most infections are asymptomatic, they are associated with increased morbidity and mortality and they also increase the cost and duration of hospitalisation. Despite a variety of prophylactic measures, satisfactory prevention of infection has not yet been achieved (Nickel *et al.*, 1984).

Previous studies have shown that bacteria gain access to the catheterised bladder by 2 routes. They either migrate to the bladder from the collecting bag or drainage tube junction within the lumen of the catheter, or they may gain access through the periurethral space outside the catheter. Refinements in the design and maintenance of urethral catheters have largely failed to reduce the incidence of catheter-associated bacteriuria. Silver has been found to have bactericidal qualities (Berger *et al.*, 1976) and it has been shown that different forms of silver coating may reduce the incidence of catheter-associated bacteriuria (Ockerblad, 1949; Lundeberg, 1986; Schaeffer *et al.*, 1988). Silver has no detrimental effect on human tissue and the use of a novel coating technique significantly reduces the toxicity of latex (Berger *et al.*, 1976; Liedberg and Lundeberg, 1989a).

The aim of this study was to establish whether a urethral catheter, coated on both inner and outer surfaces with silver alloy by means of the new technique, could prevent the transmission of infection as described above.

Patients and Methods

The study group comprised 120 of 223 in-patients who required urethral catheterisation. Criteria for selection were that the patients should have no evidence of bacteriuria at the time of catheterisation, that they should not be on antibiotic treatment and that catheterisation would not be required for more than 6 days. All were over 18 years of age, had given informed consent and were not undergoing other invasive urinary tract procedures.

The patients were randomised to receive either a silver coated latex Foley's catheter (n = 60) or a Teflonised latex Foley's catheter (Bard Ltd) (n = 60). The rest of the patients (n = 103) were excluded because of exposure to antibiotics, diabetes, etc. There was no change in brand of catheter, size or composition during the study period. Catheterisa-

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tion was performed by experienced nurses using the same sterilisation procedure in each case. The catheters were maintained according to standard guidelines for urinary drainage. Progress was monitored daily and any disconnection of the catheter drainage tube junction or improper positioning of the drainage bag was recorded.

A urine specimen was taken from the catheter for culture at the time of catheterisation. Specimens were also taken daily from the catheter sampling port by aseptic needle aspiration, and from the drainage bag 3 to 9 h after the bag was last emptied.

All urine specimens were immediately refrigerated and aliquots of 0.001 ml were streaked on sheep blood agar and McConkey agar. Colony counts were recorded after incubation for 24 h at 35°C (Stark and Maki, 1984). Standard microbiological methods were used to identify all organisms isolated and antibiotic sensitivity was tested. Significant bacteriuria in catheter specimens was defined as $>10^5$ organisms/ml). Infection rates were compared by the χ^2 test or Fischer's exact test. All patients underwent a daily physical examination.

Results

Details of the patients are given in Table 1. There was a significant difference in the infection rates between the 2 groups after 6 days' catheterisation (Fig.). Six patients (10%) with the silver coated catheter and 22 (37%) with the Teflonised latex catheter developed bacteriuria ($P<0.01$).

A total of 79 microbial species was recovered in colony counts from the 28 patients who developed bacteriuria (Table 2); 18 patients were infected by a single species and 4 by 2 organisms simultaneously.

Table 1 Details of Patients

	Groups	
	Teflonised (N=60)	*Silver alloy (N=60)*
Mean age (years)	52	48
Male	43	40
Female	17	20
Department: Urology	31	28
Surgery	29	32
Reason for catheterisation		
Haemodynamic monitoring	4	3
Post-operative drainage	56	57
Incidence of breaks in technique		
Improper bag position	5	3
Break in catheter drainage	6	4

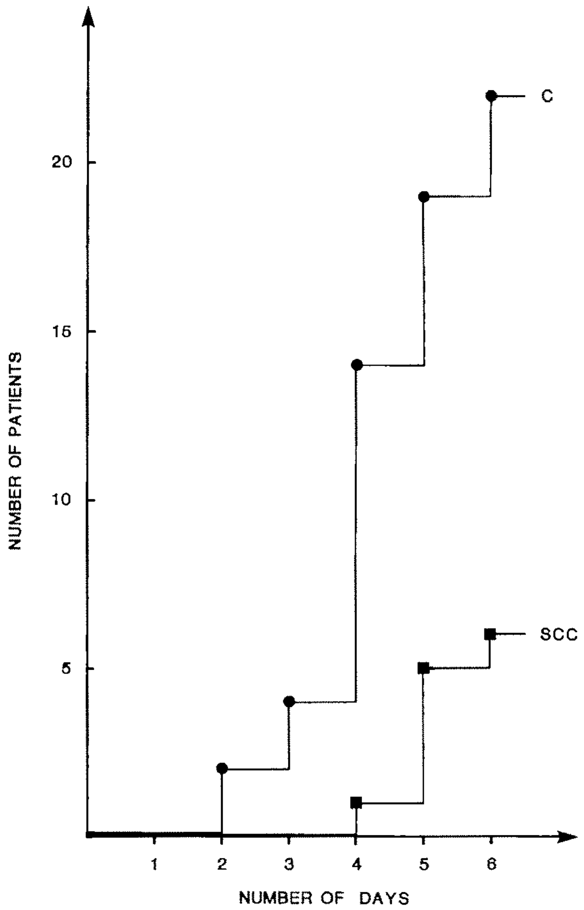

Fig. Cumulative curve of catheter-induced bacteriuria. C = Teflonised latex Foley's catheter. SCC = Silver alloy coated Foley's catheter.

Microbial contamination of urinary drainage bags was documented in 28 of the 120 patients (43%) and the most common micro-organism was *Escherichia coli*. Of the 28 bag contaminations, 24 were noted after the documentation of bacteriuria caused by the same species. The remaining 4 bags probably represent exogenous contamination. The

Table 2 Aetiology of Catheter-associated Bacteriuria

	Groups	
Organism ($\geqslant 10^5$ colonies/ml)	*Teflonised (N=22)*	*Silver alloy (N=6)*
Escherichia coli	55	12
Candida species	2	—
Pseudomonas aeruginosa	2	—
Group B streptococci	5	—
Coagulase-negative staphylococci	3	—

microbial species recovered from these 4 bags was *Escherichia coli*. The number of urine contaminations was evenly distributed throughout the 2 groups.

Ward and room assignments were monitored daily and no patient occupied a room with another catheterised patient. Since only 6 nursing units were used, several of the catheterised patients stayed in the same unit, but no instance of cross-infection was found.

Discussion

Approximately 15% of hospital in-patients receive an indwelling catheter (Kunin, 1975) and approximately 30% of patients catheterised in hospital develop bacteriuria (Jepsen *et al.*, 1982; Hart, 1985). Although many infections appear to resolve spontaneously either on removal of the catheter or with antibiotic treatment, the long-term effects of infection are difficult to establish and they have been the subject of much controversy (Guinan *et al.*, 1969).

The results of the present study show that there is a significant decrease in the tendency to develop urinary tract infection when a silver alloy coated, indwelling catheter is used rather than a standard one. This contrasts favourably with the results obtained from the use of other refinements in the design and maintenance of catheters, *e.g.* metal disinfection (Burke *et al.*, 1981), antibacterial urethral lubricants (Kunin and Finkelberg, 1971), antibiotic-impregnated catheters (Butler and Kunin, 1968) and prophylactic antimicrobial bladder irrigation (Warren *et al.*, 1978). Recent results have shown that coating catheters with a silver alloy significantly reduced their toxicity (Liedberg and Lundeberg, 1989a). It has also been shown that *Pseudomonas aeruginosa* will not grow on silver-coated catheter latex and the potential for bacterial transmission is reduced (Liedberg and Lundeberg, 1989b).

In addition to the reduction in morbidity and mortality made possible by the use of catheters coated with silver alloy, our results indicate that the economic benefits might be considerable.

Acknowledgements

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Comparative Trial of Sclerotherapy for Hydroceles

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Summary—We present a prospective single-blind trial of sclerotherapy for hydroceles with tetradecyl sulphate and rolitetracycline as sclerosants. Twenty-seven hydroceles were treated with tetradecyl sulphate and 28 with rolitetracycline. The median follow-up was 13 months. There were no statistically significant differences between the 2 drugs in respect of cure rate and complications. The overall cure rate for both drugs was 96%. Complications were rare and common to both drugs. Tetradecyl sulphate and rolitetracycline were found to be equally effective as sclerosants.

Sclerotherapy is an effective form of treatment for hydroceles. There appears, however, to be no consensus as to the most effective sclerosant and no previous studies have evaluated, in a randomised trial, different sclerosants. Several drugs have been reported to be suitable, including phenol (Nash, 1984), tetradecyl sulphate (Macfarlane, 1983), tetracycline (Hu *et al.*, 1984; Badenoch *et al.*, 1987; Bullock and Thurston, 1987) and ethanolamine oleate (Hellstrom *et al.*, 1986).

Tetracycline and tetradecyl sulphate are well accepted as sclerosants in the treatment of hydrocele (Hu *et al.*, 1984; Macfarlane, 1983) and both drugs are cheap and commercially available. Rolitetracycline is available with pre-mixed lignocaine, making preparation of the drug very simple. It has also been claimed that tetracycline is superior because of its antibiotic properties (Bødker *et al.*, 1985). A randomised comparative trial of rolitetracycline versus tetradecyl sulphate as sclerosants in hydrocele sclerotherapy was performed in order to establish which drug was more effective.

Patients and Methods

A prospective randomised single-blind trial of sclerotherapy was initiated. Of 68 consecutive patients with 90 hydroceles seen in this department, 19 were excluded because of concomitant ipsilateral inguinal hernia, suspicion of malignancy or tuberculosis, ipsilateral persistent processus vaginalis and epididymo-orchitis in the preceding 3 months. There was no age limit. Patients gave informed consent and were offered sclerotherapy or surgery. They were randomised to receive 1 of the 2 sclerosant solutions and those with bilateral hydroceles received both solutions, 1 drug being used for each hydrocele during the same out-patient visit.

Tetradecyl sulphate was used in the form of 3% sodium tetradecyl sulphate solution (STD, STD Pharmaceuticals, Hereford); 2% lignocaine was added to the tetradecyl sulphate in a ratio of 1 ml lignocaine to 5 ml tetradecyl sulphate to obtain a concentration of local anaesthetic of 0.33%. The tetracycline used was rolitetracycline 3.5% (Reverin, Hoechst Pharmaceuticals, Johannesburg, South Africa). This is available as a powder with 350 mg rolitetracycline and 40 mg lignocaine; 10 ml sterile water were added to the powder, producing a solution of 3.5% rolitetracycline and 0.4% lignocaine.

The procedure was carried out under sterile conditions in the out-patient department. The hydrocele was rendered tense by manual compression and was entered with an 18 gauge radiopaque intravenous infusion cannula and needle (Jelco, Ethicon SPA, Rome, Italy). The puncture was made in the upper portion of the hydrocele in a relatively avascular area. No local anaesthetic infiltration of the subcutaneous tissue was per-

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formed. The needle was removed and the hydrocele aspirated via the cannula using a 50 ml syringe. Complete emptying was achieved by manipulation of the scrotum if necessary. The volume of fluid aspirated was recorded and biochemically evaluated for electrolyte, urea, creatinine, total protein and albumin content. The fluid was subjected to microscopy and culture (including culture for *M. tuberculosis*). Patients whose hydrocele fluid was macroscopically blood stained were referred for surgical exploration. The volume of sclerosant injected was dictated by the volume of hydrocele fluid aspirated (Table 1). The sclerosant was injected via the cannula, which was then removed and the scrotum massaged to ensure even distribution of the sclerosant. A scrotal support was applied for 48 h. Patients were told that some reaccumulation might occur, especially during the first week.

Re-evaluation was carried out 1 month later. If there was no recurrence, or a recurrence <25 ml was present, no further treatment was given and the patients were seen 3 months and again 12 months after the procedure. If a larger recurrence was present, repeat sclerotherapy with the same sclerosant was applied at monthly intervals until a cure was obtained, or the patient requested or required surgery, or until 5 monthly sclerotherapy sessions had failed to effect a cure. Once the hydrocele was cured the patients were seen 3 months and 12 months later.

Patients were assessed for pain 5 min after sclerotherapy and at follow-up 1 month later. Pain was assessed on an arbitrary scale: nil, minimal, moderate, severe and excruciating (requiring hospitalisation). At follow-up, close attention was paid to the amount of residual induration. All sclerotherapy was administered by R.K.R. and follow-up was performed by the same person.

Results

A total of 67 hydroceles were studied. Four patients with 6 hydroceles died of unrelated causes during the follow-up period. Another 4 with 6 hydroceles failed to attend for follow-up and were excluded from analysis of the results. Thus 27 hydroceles were treated with tetradecyl sulphate and 28 with rolitetracycline. The median age of the patients was 57 years (range 16–82). The median volume of fluid aspirated was 157 ml (range 15–1393). The median follow-up period was 13 months (range 3–17). The 2 groups were compatible with respect to age, volume of fluid aspirated and length of follow-up.

Table 1 Volume of Sclerosant

Volume of fluid aspirated from hydrocele (ml)	*Volume of sclerosant instilled into hydrocele (ml)*
0–100	5
101–500	10
501–750	15
751–1000	20
1001–1250	25
1251–1500	30

The results are summarised in Table 2. Cure was defined as complete disappearance of clinically detectable hydrocele and patient satisfaction. The total cure rate was 96% and both drugs were equally effective.

Of the 27 hydroceles treated with tetradecyl sulphate, 5 patients (19%) experienced more than mild pain. Of the 28 hydroceles treated with rolitetracycline, 11 (39%) experienced more than mild pain. The difference between the degrees of pain was not statistically significant. An acute inflammatory reaction occurred in 5 hydroceles in 4 patients. This consisted of fever, severe scrotal pain and scrotal tenderness. Three of these hydroceles were treated with tetradecyl sulphate and 2 with rolitetracycline. A residual mass or induration developed in the majority of cases. No objective means of measuring the induration was used and no accurate statistics were drawn up. However, in most cases the residual mass disappeared within 3 months.

Two patients underwent surgery because of multilocular hydrocele formation. One had had tetradecyl and the other tetracycline sclerotherapy. A radical hydrocelectomy was performed and they were considered sclerotherapy failures. Both had post-operative oedema and haematoma, but the

Table 2 Results of Sclerotherapy

	No. of patients (%)	
Results	*Tetradecyl sulphate*	*Rolitetracycline*
Cured by sclerotherapy		
Single injection	17 (63)	18 (64)
Two injections	5 (18)	5 (18)
Three injections	3 (11)	4 (14)
Four/more injections	1 (4)	0 (0)
Total	26 (96)	27 (96)
Sclerotherapy failed (cured by hydrocelectomy)	1 (4)	1 (4)
Total cured	27 (100)	28 (100)

operation was not technically more difficult because of the prior sclerotherapy and the results were satisfactory.

One other patient developed a multilocular hydrocele after tetradecyl sclerotherapy but refused hydrocelectomy. On follow-up 1 year later he had mild asymptomatic induration around the testis but was satisfied with the result. None of the biochemical or microbiological studies showed statistical differences.

Discussion

Previous trials of sclerotherapy for hydroceles have, with some exceptions, shown the efficacy of this modality (Nash, 1984; Hu *et al.*, 1984; Badenoch *et al.*, 1987). The present study revealed no significant differences in the total cure rate or the incidence of complications in hydroceles treated with either rolitetracycline or tetradecyl sulphate. Most studies using tetradecyl sulphate have reported a cure rate of around 95% (Macfarlane, 1983) and those using tetracycline cure rate of 90% and above (Levine and De Wolf, 1988; Bullock and Thurston, 1987; Hu *et al.*, 1984). Our cure rate of 96% compares favourably with the above results.

The complications of sclerotherapy have generally been infrequent and minor. Notable exceptions were the studies by Thomson and Odell (1979) and Badenoch *et al.* (1987). The former reported a 50% failure rate, with 80% of these failures requiring surgery. The latter reported a recurrence rate of 67% and severe pain associated with the procedure. Our complications were limited to severe pain, acute inflammatory reaction and multilocular hydrocele formation. No abscess formation, skin necrosis, testicular injury or loss of the testis occurred. This is in keeping with most of the recently reported studies. The occurrence of pain after sclerotherapy was more common after tetracycline than after tetradecyl sulphate but the difference was not statistically significant. We did not use a spermatic cord block or scrotal skin infiltration and found that simultaneous instillation of local anaesthetic and sclerosant into the hydrocele sac was satisfactory. The lack of sepsis in either drug group appears to invalidate the claim that tetracycline is better because of its antibacterial activity (Bødker *et al.*, 1985; Levine and De Wolf, 1988).

Multilocular hydrocele formation has been reported by Rencken *et al.* (1987). In our study, both tetracycline and tetradecyl caused this complication. The histological findings in our 2 patients were similar. Both had fibrin deposition with multiple fibrinous septae as described by Hu *et al.* (1984), which seems to indicate that the aetiology of this complication is not related to one specific drug.

An acute inflammatory reaction after sclerotherapy was common to both drugs but in all cases the hydroceles were cured. The aetiology of the condition is unclear, but cannot be attributed specifically to just one of the two drugs used in this study.

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Is Routine Primary Retroperitoneal Lymph Node Dissection Still Justified in Patients with Low Stage Non-seminomatous Testicular Cancer?

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Summary—We present 8 years' experience of primary retroperitoneal lymph node dissection (RLND) in 190 patients with low stage non-seminoma; 154 patients had clinical stage I (CSI) and 36 had clinical stage IIa (CSIIa) disease. Of the 154 patients with CSI tumours, 33 had increased serum AFP and/or HCG before RLND (CSIM+) and 121 had normal tumour markers (CSIM−).

Retroperitoneal lymph node metastases (pathological stage II) (PSII) were found in 38 of 121 patients with CSIM−, in 19 of 33 patients with CSIIM+ and in 26 of 36 patients with CSIIa. In a multivariate analysis, the presence of small vessel infiltration (demonstrated in histological sections of the primary tumour) and a prolonged tumour marker half-life were predictive factors for PSII. These 2 factors enabled a group of non-seminoma patients with CSI disease to be identified who had a 15% risk of retroperitoneal tumour growth (low risk group) as compared with a high risk group where 60 to 70% of patients had retroperitoneal lymph node metastases.

Relapses occurred in 7 of 107 patients with PSI and in 6 of 83 patients with PSII disease; in the latter group, 5 relapses developed before the start of routine adjuvant chemotherapy; 6% of patients developed major post-operative complications. In addition, "dry ejaculation" was the principal side effect following RLND (unilateral RLND: 20/132 patients; bilateral RLND: 50/54 patients).

The comparative cost to the health service during the first year of follow-up was estimated for low risk non-seminoma patients with CSI subjected to RLND and for those in whom a surveillance policy was adopted. The latter approach was preferable.

It was concluded that a surveillance policy should be followed in low risk non-seminoma CSI patients provided that frequent follow-up is possible. A more active policy is recommended in high risk patients (*e.g.* adjuvant chemotherapy without RLND). Nerve-sparing RLND may be considered in patients with CSIIa disease and negative tumour markers.

The treatment of low stage non-seminomatous testicular cancer (NSTC) has changed considerably during the last 15 years. In the 1970s all patients were treated with radiotherapy or surgery in addition to orchiectomy, the choice depending on the policy of the individual treatment centre (Clements *et al.*, 1981; Van der Werf Messing and Hop, 1982; Whitmore, 1982; Fosså *et al.*, 1984; Fraley *et al.*, 1984; Von der Maase *et al.*, 1984). In the 1980s some oncological centres introduced a "wait and see" or surveillance policy in patients with no clinical or radiological evidence of metastases, *i.e.* CSI (Glatstein, 1979; Peckham *et al.*, 1982; Pizzocaro *et al.*, 1985b; Herr *et al.*, 1986; Freedman *et al.*, 1987). These patients were followed up after inguinal orchiectomy without further treatment and received salvage therapy in case of relapse. Such a surveillance policy requires frequent

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follow-up and costly examinations such as CT. Unfortunately, these requirements cannot always be met and the Norwegian Radium Hospital, together with other oncological centres, therefore pursued a more active treatment policy (Fosså *et al.*, 1984) until 1987, when a surveillance policy was introduced for selected patients with CSI disease.

This study analyses our experience with primary RLND in NSTC and discusses the results in the light of our preliminary experience with the surveillance policy.

Table 1 Details of Patients

	CSI		*CSIIa*
	M−	*M+*	
No. of patients	121	33	36
Age (years)	29* (16–64)†	26 (15–49)	31 (18–64)
Histology			
Malignant teratoma, differentiated	9		4
Malignant teratoma, intermediate	70	25	22
Malignant teratoma, undifferentiated	37	5	10
Malignant			
teratoma, trophoblastic	4	3	
seminoma (AFP-producing)	1		
Presence of yolk sac elements	54	25	20
PT category 1	84	23	26
>1	37	10	20
Small vessel invasion			
No	90	19	18
Yes	31	14	18
Tumour markers prolonged half-life	10/56‡	16/31	12/19
AFP and/or HCG elevated			
before orchiectomy	26/43	14/15	10/14
before RLND	0	33	15
Interval between orchiectomy and RLND (days)	34 (13–110)	35 (12–71)	36 (6–60)

* Median. † Range. ‡ Observed/evaluated.

Patients and Methods

From 1979 to 1986, 190 patients with low stage NSTC underwent primary RLND. They were staged according to the Royal Marsden classification system based on clinical and radiological examinations (Peckham *et al.*, 1979). Computed tomography showed the maximal diameter of the largest lymph node to be less than 20 mm in all patients. A patient was considered to be in stage IIa if at least 1 node exceeded 15 mm in maximum transverse diameter or if 2 or more nodes exceeded 10 mm (Lien *et al.*, 1983). All other patients in the series were considered to be stage I. Using these criteria, 154 patients were CSI and 36 CSIIa (Table 1). CSI patients were further subdivided according to the level of tumour markers (human choriogonadotrophin (HCG) and/or alpha-fetoprotein (AFP)) before RLND; 121 patients with normal tumour markers were placed in category CSIM −; the remaining patients with AFP ≥ 20 μg/1 or HCG ≥ 10 u/1 were placed in category CSIM+. The half-life of serum AFP and HCG was also estimated if more than one post-orchiectomy tumour marker assessment was performed. Prolonged half-life times were defined as >6 days for AFP and >2 days for HCG. Patients who had undergone orchiectomy between February 1981 and February 1986 were included in the Swedish/Norwegian Testicular Cancer Project.

The histology of the primary tumour was revised by one of the authors (A.E.S.) according to Collins and Pugh (1964) and Mostofi and Sobin (1977). For each tumour the presence of small vessel invasion was assessed without discriminating between lymphatic and blood vessel involvement.

Initially, unilateral RLND was carried out only in patients who per-operatively proved to be tumour-free (Fosså *et al.*, 1984). During the final period of the investigation, unilateral RLND was also performed in some patients with very limited metastatic tumour burden. All other patients in pathological state II (PSII) underwent bilateral RLND. Eighty-one patients with viable retroperitoneal metastases were given 2 to 4 cycles of cisplatin-based chemotherapy (2 cycles, 7 patients; 3 cycles, 40; 4 cycles, 34). Two patients with totally necrotic lymph node metastases received no adjuvant chemotherapy.

Patients who had undergone RLND were reviewed every 2 months for the first 18 months and every 3 to 4 months for the following 18 months. Two yearly follow-up visits were scheduled during the fourth and fifth post-operative years. Routine follow-up investigations included clinical examination, chest X-ray and determination of serum tumour markers (upper limits of the normal range: AFP 20 μg/1, HCG < 10 u/1). In clinically tumour-free patients, routine abdominal CT was performed 2 months after RLND.

Seventeen patients who were included in the surveillance protocol have now been followed up for at least 1 year. They were seen monthly during this period and received abdominal and thoracic CT at 2, 4, 8 and 12 months.

Statistics

The χ^2 test was applied to analyse univariate distributions. Multivariate analysis was performed according to Cox.

Results

Fifty-seven of the 154 patients with CSI (37%) and 26 of the 36 patients with CSIIa (72%) were in pathological stage II (Table 2). In the 121 patients with CSIM−, 38 (31%) had retroperitoneal tumour growth. Unilateral RLND was done in 107 patients with PSI and in 28 patients with PSII.

Between 1 and 14 metastatic lymph nodes were removed in patients with PSII, the largest diameters ranging from < 1 to 45 mm. In 8 PSII patients the largest diameters fo the metastatic foci were 1 mm or less, the smallest being 0.3 mm. In 4 of the 38 patients with CSIM− but PSII, the largest metastatic lymph node measured more than 2 cm.

Eight of the 107 patients with PSI and 6 of the 83 patients with PSII had a recurrence (Table 2). Five relapses in patients with PSII developed within 4 weeks of RLND, before adjuvant chemotherapy could be started. All recurrences were observed within the first 2 post-operative years. All relapses were diagnosed by chest X-rays, clinical examination and/or tumour marker determination. No retroperitoneal relapse was observed. All patients with recurrent tumours received cisplatin-based chemotherapy (4 cycles) and were cured.

Table 2 Results

	CSI		*CSIIa*
	M− *(121)*	*M+* *(33)*	*(36)*
Pathological stage			
I	83	14	10
IIa	29	11	13
IIb	9	8	13
Type of RLND			
Unilateral	98	20	17
Bilateral	23	13	19
No. of metastatic lymph nodes	2*	3	2
	(1–6)†	(1–6)	(1–14)
Largest diameter	9	16	18
Lymphatic metastasis (mm)	(<1–40)	(1–28)	(1–45)
No. of recurrent patients	9	2	3
Sites: marker only	2	2	1
lung only	3		
lung + marker	3		
inguinal	1		
mediastinal			2
Interval RLND-relapse	91		40
(days)	(39–621)	(5–27)	(39–171)

* Median. † Range.

Table 3 Post-operative Ejaculatory Function and Type of RLND

	Ejaculation		
RLND	*Normal*	*Dry*	*Total*
Unilateral	112	20	132
Right-sided	65		65
Left-sided	47	20	67
Bilateral	4	50	54
Total	116	70	186*

* 4 patients not evaluable.

Two patients died but the cause of death was unrelated to cancer. The cancer-corrected survival rate was thus 100% after a median observation time of 70 months (range 26–116).

The following major post-operative complications were observed: clinically symptomatic retroperitoneal lymph cyst 5, retroperitoneal haemorrhage 1, thrombosis 2, atrophy of the left deltoid muscle 1 (probably due to per-operative nerve injury caused by the patient's position during RLND), ileus 1. One patient, operated on in 1983, received HIV infected plasma during the post-operative course. All Norwegian blood products are now routinely tested for HIV.

Post-operative "dry ejaculation" was reported by 70 of 186 patients (4 patients were not evaluable) (Table 3). No patient developed this complication after right-sided RLND, but it was found in 30% (20 of 67) after left-sided RLND.

In a univariate analysis performed in the 154 patients with CSI, the following factors predicted the presence of PSII (Table 4): prolonged post-orchiectomy half-life for tumour markers; increased AFP/HCG before RLND; small vessel invasion; PT category > 1, absence of yolk sac elements in the primary tumour (only in CSIM− cases). In a multivariate analysis, only prolonged half-life of the tumour markers and the presence of small vessel infiltration were recognised as independent factors predictive of PSII. The predictive significance of these 2 risk factors was strong: if neither was present, only 14% of patients had PSII. Prolonged tumour marker half-life alone predicted PSII in 75% of cases; 66% of patients with small vessel invasion but normal tumour marker half-life had PSII. If both risk factors were present, 97% of patients had retroperitoneal lymph node metastases.

Table 4 Prediction of Pathological Stage in CSI Patients. Distribution of Clinical and Histopathological Parameters in PSI and PSII Patients

	CSI			
	M−		*M+*	
	PSI (83)	*PSII (38)*	*PSI (14)*	*PSII (19)*
Prolonged half-life of AFP/HCG				
Yes	2	8*	2	14*
No	38	8	11	4
Elevated AFP				
Yes			12	18
No			2	1
Elevated HCG				
Yes			3	6
No			11	13
Small vessel invasion				
Yes	8	23*	4	10
No	75	15	10	9
pT category				
1	64	20*	11	12
>1	19	18	3	7
Embryonal carcinoma elements				
Yes	66	32	9	14
No	17	6	5	5
Yolk sac elements				
Yes	42	12*	10	15
No	41	26	4	4

* $P<0.05$.

Discussion

A 25 to 30% rate of patients with CSI but PSII is in accordance with other published studies (Thomas *et al.*, 1981; Richie *et al.*, 1982; Rowland *et al.*, 1982; Samuelsson *et al.*, 1986). The frequency of PSII in NSTC CSI depends on the radiological criteria for CSI. These are not always defined in other published studies. It has been shown by Lien *et al.* (1986) and Stomper *et al.* (1987) that the false-positive rate of abdominal CT increases significantly if one decreases the critical lymph node size defined as indicative of metastases. Bipedal lymphography increases the pre-operative diagnostic accuracy rate only to a limited extent (Lien *et al.*, 1983). The influence of the radiological technique (contiguous versus non-contiguous scan reading) had been investigated previously and was found to be limited (Lien *et al.*, 1987).

The relatively high percentage of PSII is indirectly supported by the surveillance study of 259 patients performed by the Medical Research Council, which confirmed that 32% of patients with CSI have micro-metastases indicated by relapse during follow-up (Freedman *et al.*, 1987). The fact that only about half of the patients from the MRC study had clinically detectable retroperitoneal lymph node metastases at the time of relapse does not exclude the possibility that most of them might indeed have had metastatic micro-foci in the retroperitoneal space, though undetectable by radiological methods. These lymphatic micro-foci would, of course, be sterilised by subsequent chemotherapy given in the event of lung metastases or increase in serum tumour markers. Relapse rates of about 30% have been reported in patients in whom a surveillance policy was adopted (Herr *et al.*, 1986; Pizzocaro *et al.*, 1985b).

It is disappointing that metastatic lymph nodes with a diameter up to 4 cm were not always recognised on abdominal CT. Our observation raises some concern about the reliability of a negative abdominal CT during follow-up of CSI patients who are included in a surveillance policy. Such concern is also expressed by the group from Milan (Pizzocaro *et al.*, 1985b, 1986).

It has been shown that about 50% of patients with limited PSII can be cured by surgery alone and do not need adjuvant therapy (Pizzocaro *et al.*, 1984; Williams *et al.*, 1987). Omitting such routine adjuvant chemotherapy in patients with PSII demands frequent follow-up in order to detect relapse at an early and still curable stage. If this is not possible, routine adjuvant chemotherapy is recommended, as given in the present study. Two cycles of chemotherapy are probably adequate for patients undergoing radical treatment (Williams *et al.*, 1987).

Our relapse rate of 7% after unilateral RLND in patients with PSI is similar to (or even lower than) that reported elsewhere after bilateral RLND (Bredael *et al.*, 1983; Fraley *et al.*, 1984). Unilateral RLND, if performed by an experienced surgeon, seems a satisfactory approach in patients with PSI.

RNLD is usually well tolerated by young testicular cancer patients, though it yields transient morbidity and is the regular cause of 6 weeks' sick leave. As shown in the present study, more serious and long-lasting side effects may occur occasionally.

The major concern of patients undergoing RLND is dry ejaculation and its impact on fertility and sex life. The results of this study confirm our preliminary observations that dry ejaculation is not a problem after right-sided RLND, but is a significant side effect in one-third of patients undergoing left-sided RLND (Fosså *et al.*, 1984). The reason for this difference is not known, but we are currently analysing patients' records in this respect. Other centres have not found such differences (Pizzocaro *et al.*, 1985a). Lange *et al.* (1987) and Donohue *et al.* (1988) showed that the frequency of dry ejaculation could be reduced significantly after both unilateral and bilateral RLND by nerve-sparing techniques.

As in the study by Freedman *et al.* (1987) and other investigations (Herr *et al.*, 1986; Hoskin *et al.*, 1986; Pizzocaro *et al.*, 1985b), small vessel invasion was a strong predictive factor for PSII or relapse during follow-up in patients included in a surveillance policy. In the present study this was the only predictive histological factor which emerged in the multivariate analysis. Freedman *et al.* (1987) found that the presence of undifferentiated cells (embryonal carcinoma elements) and the absence of yolk sac elements were also indicative of subsequent relapse, indicating the presence of micro-metastases at the time of diagnosis. The difference may be explained by the different numbers of patients in the 2 studies and by the fact that we included patients with prolonged tumour marker half-life times in the multivariate analysis. This feature was another important predictive factor for the presence of retroperitoneal lymph node metastases, even in patients who finally achieved normal AFP/HCG levels before RLND. These observations underline the need for multiple determinations of AFP/HCG before and after orchiectomy. Patients with significantly prolonged tumour marker half-life times should be excluded from the surveillance policy (Hoskin *et al.*, 1986).

Should primary RLND still be used in the treatment of low stage NSTC or is a surveillance policy preferable? Both policies lead to a 100% cure rate provided that follow-up routines are adequate. After RLND, follow-up is straightforward (chest X-ray, tumour markers, clinical examination), especially if adjuvant chemotherapy is given routinely to patients with PSII.

Many of the follow-up examinations can be performed at local hospitals rather than specialised oncological centres. However, the morbidity rate after RLND and particularly the risk of dry ejaculation cannot be overlooked. We cannot explain the significant difference between patients undergoing right- and those undergoing left-sided unilateral RLND. The surveillance policy may be advantageous in cases where dry ejaculation would lead to major psychological distress. On the other hand, the frequent but essential follow-up visits can be difficult to organise over a period of 3 to 5 years and may cause considerable psychological problems (Pizzocaro *et al.*, 1985b; Zanoni *et al.*, 1987).

A compromise in this situation is to apply the surveillance policy in non-seminoma patients with CSI and low risk factors (no small vessel involvement of primary tumour, normal half-life of AFP/HCG), provided that frequent and regular follow-up visits are possible. Anticipating that a similar failure rate (PSII or subsequent relapse) occurs in low risk patients with CSI as in those following the surveillance policy (about 15%), the estimated minimum health service expenses for follow-up during the first year after diagnosis favour the surveillance policy (Table 5).

In the high risk group of CSI non-seminoma patients, active management is recommended. Since 60 to 70% have micro-metastases, it seems justifiable to omit routine RLND and to give a few cycles of adjuvant chemotherapy, thus preserving normal ejaculation. Patients with consistently elevated tumour markers should receive chemotherapy. RLND is unnecessary in these patients. The treatment of CSII should probably be more invidualised. In patients with negative tumour markers who are unwilling to take the risk of post-operative dry ejaculation, chemotherapy alone will usually be successful. In other situations (*e.g.* older patients with no plans for further children), primary staging RLND is recommended, followed by adjuvant chemotherapy in cases of PSII. Since 28% of patients with CSIIa have no tumour in the retroperitoneal space, there is a need to define predictive factors for this subgroup by future analyses.

Table 5 Estimated Minimum Health Service Expenses for First Year of Follow-up in Low Risk Non-seminoma Patients with CSI. (Expected failure rate 15% in both groups)

	RLND		*Surveillance*	
Resource	*Details*	*NOK**	*Details*	*NOK**
Diagnosis				
RLND/Hospitalisation	10 days	20000	—	—
Sick leave	6 weeks	14000	—	—
Follow-up				
Sick leave	6 days	2000	12 days	4000
Abdominal CT	× 1	1000	× 4	4000
Thoracic CT	—		× 4	4000
Chest X-ray	× 6	900	× 8	1200
Marker determination	× 6	1100	× 12	2200
Clinical examination	× 6	900	× 12	1800
Travel expenses	550 km	1400	1300 km	3300
Total		41300		20500

* NOK = Norwegian krowns.

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Gravity Cavernosometry—a Simple Diagnostic test for Cavernosal Incompetence

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Summary—The papaverine test has been widely used as a diagnostic procedure in erectile impotence. However, when patients do not achieve full erection on the test, it is necessary to differentiate between insufficient inflow and excessive outflow.

Gravity cavernosometry is a method designed to evaluate the pressure responses in the corpora when they are subjected to a constant infusion pressure. The infusion flow is of minor significance.

The intracavernous pressure (ICP) was measured in cadavers, in psychogenically impotent patients and in patients with arteriogenic impotence, following administration of papaverine and gravity perfusion.

During perfusion in cadavers and in psychogenic patients, the ICP showed values above 110 cm H_2O, while in arteriogenic patients the values ranged from 30 to 141 cm H_2O. In the arteriogenic group, 11/20 patients had an ICP lower than 110 during perfusion. There was no correlation between the pre-perfusion pressure and the final pressure with perfusion.

Gravity cavernosometry is a simple, cost-effective and reliable method for the assessment of corporeal competence.

When patients fail to achieve full erection during the papaverine test, a distinction must be made between insufficient inflow and excessive outflow. The competence of the veno-occlusive mechanism of the corpora cavernosa has been assessed by means of dynamic infusion cavernosography. The method involves measuring the flow rates required to promote and to maintain erection, as well as radiographic visualisation of the outflow routes from the corpora cavernosa. Most authors base the diagnosis of venous leakage solely on quantification of the flow; the cavernosogram is used simply to visualise the veins. Roller pump perfusion, with and without papaverine administration, has been described as the most popular method of establishing the rate of flow required to obtain and maintain erection, but the standards for these measurements remain controversial (Newman and Reiss, 1984; Virag *et al.*, 1984; Wespes *et al.*, 1984; Buvat *et al.*, 1986; Desai *et al.*, 1988). In non-relaxed cavernous tissue, erection may be produced with a pump at a fixed flow rate, but with an infusion pressure much higher than physiological arterial pressures. The rigidity of erection is related to intracavernous pressure rather than flow rate; the outflow rates at full erection vary considerably between individuals, and even men with large outflow pathways are able to achieve erections if the arteries can provide the required inflow rates.

Evaluation of the flow rates necessary to maintain erection with infusion pumps does not consider the arterial flow (always unknown), which increases during artificial erection even in the absence of vasodilator drugs (Michal *et al.*, 1980). Outflow measurements at ICPs greater than the arterial systolic pressure can eliminate this problem (Goldstein, 1987), but perfusion with supraphysiological pressures may artificially create increased venous outflow and could damage the delicate structure of the corpora. In addition, the pumps and transducers are expensive and not available to many physicians.

Erection depends on the increase in ICP, which demands high pressure in the arteries feeding the

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sinusoids and competence of the veno-occlusive mechanism (Fournier *et al.*, 1987). The ICP during erection is the result of the mean arterial pressure less the pressure lost through the venous drainage system. Patients whose arteries do not provide a high pressure, due to organic or functional impairment, cannot achieve high ICPs on papaverine testing. In such cases it is useful to know how the corpora behave when the inflow pressure is elevated to normal levels. When a cavity is submitted to fluid infusion from different sources, internal pressure tends to equal that of the source with the highest pressure, and how closely it approaches the infusion pressure depends on the ratio between the calibre of inflow and outflow pathways.

The principle of gravity cavernosometry is to provide a source of inflow with a constant pressure similar to the mean arterial pressure (Lue *et al.*, 1984). This inflow is added to the arterial inflow, so that if the pressure in the arteries feeding the corpora is low, the infusion set provides the additional infusion pressure. Since the calibre of the needle used is always the same, comparison between individuals is possible.

The aim of the present study was to describe the technique of gravity cavernosometry and to report the results obtained in the evaluation of various groups of patients.

Patients and Methods

The study included 10 cadavers, 20 psychogenically impotent (PI) patients and 20 impotent patients with arterial insufficiency (AI). All patients in groups PI and AI were non-responders in the papaverine test and were selected from a larger series of consecutive patients after exclusion of papaverine responders, since patients who achieve rigid erections after papaverine injections are considered to have a competent veno-occlusive mechanism and do not require cavernosometry. The ages in the cadaver group ranged from 25 to 52 years (mean 40.4); in the PI group they varied from 25 to 53 years (mean 39.3) and in the AI group from 46 to 72 years (mean 57.4).

The diagnosis of psychogenic impotence was based on history and psychological interview with both the patient and his partner. All 20 patients reported difficulty in obtaining or maintaining erections in some (but not all) circumstances. Ten of 20 patients reported impotence occurring with a specific partner, but not with others. Six claimed to have periods of impotence and periods of normal sexual activity which were related to events such as vacations or professional success. Four reported normal erections at masturbation but complete absence of erection on sexual intercourse; 3 obtained complete relief of their erectile disability after some weeks of psychological counselling. All reported rigid nocturnal erections. None had diabetes, hypertension or were undergoing treatment for any other disease.

The 20 patients in the AI group had a penile-brachial index <0.7; 9 also had intermittent claudication, 4 had diabetes and 2 had coronary atherosclerotic disease. Although pudendal angiography was suggested to all patients in this group, only 11 agreed to the procedure. Arterial obstruction was demonstrated in each case.

Gravity perfusion was performed in all patients as described below. Papaverine (100 mg) was administered intracavernously 20 min before the procedure.

Technique

Two 19 gauge needles were placed, 1 in each corpus. One was connected to a column of saline, for ICP measurement in cm H_2O; the other was connected to a flask 140 cm above the level of the penis, for intracavernous infusion of warm saline. The ICP was measured initially with the infusion line closed and then completely open. The infusion produced an increase in ICP; after a plateau had been reached, the infusion flow was determined by means of a cronometer and the time needed to infuse 100 ml was calculated. This determined flow rate was compared with the expected flow on that pressure gradient (Table), so that the examiner could be certain that the infusion line was unobstructed.

Table Expected Flow Delivered by a 19 Gauge Needle Submitted to Different Pressure Gradients (approximate)

Pressure gradient (cm H_2O)	*Flow (ml/min)*
10	5
20	10
30	15
40	20
50	25
60	30
70	35
80	40
90	45
100	50
110	55
120	60
130	65
140	70

Results

The ICP values obtained in the cadavers and in the 2 groups of patients are shown in the Figure. There was no significant difference between cadavers and PI patients with perfusion ($P<0.05$). AI patients, when submitted to perfusion, showed a wide range of values.

There was no correlation between ICP with and without perfusion in each group (Kendall's correlation index = 0.05 in the PI group, 0.22 in the AI group).

All of the patients with psychogenic impotence had ICPs > 110 cm H_2O after perfusion.

Discussion

The difference between pump and gravity perfusion is that the flow rate in the former is determined by the examiner and the inflow pressure is determined by the pump; in the latter, the inflow pressure is determined by the examiner and the flow rates are determined by the compliance of the corpora. When gravity perfusion is performed, the ICP tends to approach the pressure provided by the elevated flask, but never equals it because some pressure is always lost through the venous drainage system. The closer the ICP and infusion pressure, the better is the status of the veno-occlusive mechanism. A flask at a height of 140 cm provides an inflow pressure higher than the commonly accepted arterial pressure to maintain a rigid erection (90 mm Hg) (Wespes and Schulman, 1984) and when a 19 gauge needle is used, the flow rate is sufficient to produce an erection in the non-contracted corpora, even in the absence of arterial inflow, as demonstrated by our results in cadavers. The data obtained in this study showed that the ICP in the PI group reached values above 110 when under perfusion. Thus it was concluded that patients who are haemodynamically able to achieve good erections respond to gravity perfusion, even when they do not have erections with the administration of papaverine alone. Similar results were not observed in all patients with arterial insufficiency: in the AI group the response to perfusion varied widely according to the competence of the veno-occlusive mechanism, which is compromised in the presence of arterial disease (Azadzoi *et al.*, 1988). In both groups, the final pressure obtained with perfusion was not related to the initial pressure for each case.

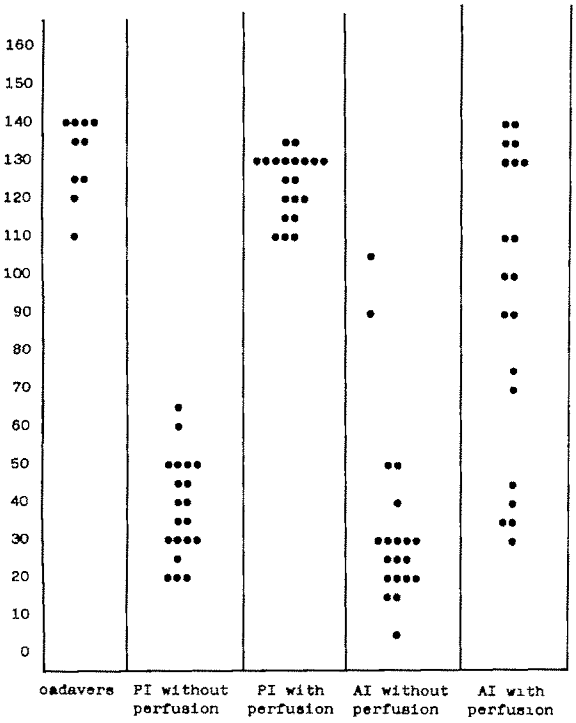

Fig. Distribution of ICP values.

When gravity perfusion is used, the flow rate is always proportional to the pressure gradient between the infusion pressure (140 cm H_2O) and the ICP. Therefore, measurement of the infusion flow is used only to verify that no obstruction is present in the infusion set, needle or sinusoids. If the measured flow is considerably lower than the expected flow to a given pressure gradient, gentle re-positioning of the needle will usually increase the flow unless severe intracavernous obstructive disease is present; in this case, cavernosography is required to complete the diagnosis.

Gravity cavernosometry is a simple, inexpensive and reliable method which may be used to assess the competence of the veno-occlusive mechanism of the corpora cavernosa. Further experience will clarify its role in clinical practice.

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Erection and Ejaculation in Man. Assessment of the Electromyographic Activity of the Bulbocavernosus and Ischiocavernosus Muscles

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Summary—Electromyographic (EMG) recordings were obtained by concentric needle electrodes from the bulbocavernosus (BC) and ischiocavernosus (IC) muscles in 7 human volunteers during excitement to erection and subsequent ejaculation. Simultaneous registration of the time course and volume of each expressed spurt of semen was obtained using an aluminium pan suspended in front of the subject's penis on a force transducer the output of which was charted with the EMG activity. The BC and IC muscles showed no EMG activity during erection and detumescence cycles induced by visual sex stimulation. In 5 of 7 subjects, the first EMG burst of the BC in ejaculations induced by masturbation was not correlated with an expelled spurt of semen as were subsequent bursts. However, only 26 to 60% of the total number of EMG bursts were accompanied by expulsion of a spurt of semen. There thus appears to be a large safety factor in the striated muscle expulsive mechanism. Oral phenoxybenzamine treatment in 2 subjects did not significantly affect either the number of EMG bursts of the BC or the subjective pleasure of the orgasm but did significantly reduce the volume of semen expelled. Semen volume does not appear to be a unique determinant of the pleasure felt or the trigger for ejaculation.

The paired, striated muscles at the base of the human penis, known as the bulbocavernosus and ischiocavernosus, have long been thought to play a role in erection and ejaculation. Varolius (1573) first proposed that their active contraction induced erection by compressing venous drainage. De Graaf (1668) also argued for this mechanism on anatomical grounds, suggesting that at ejaculation the contractions of the bulbocavernosus muscle would compress the urethra and expel its contents. Subsequent descriptions of human ejaculation have included the contractile activity of the bulbocavernosus muscle (Masters and Johnson, 1966; Kedia and Markland, 1976; Newman *et al.*, 1982; Reckler, 1983; Kothari, 1984; Benson, 1988) and even that of the ischiocavernosus muscle (Bancroft, 1983; Kothari, 1984; Benson, 1988) in the forceful ejection of semen. Brindley (1985), however, thought that the contractions of the ischiocavernosus muscle were of no importance in relation to ejaculation. A recent review (Sachs and Meisel, 1988) discussed the lack of critical experiments in the human field. Despite this long history, actual measurement of the activity of either muscle was not attempted until Kollberg *et al.* (1962) published electromyographic records of the bulbocavernosus muscle during ejaculation followed by a report on muscle contractions of the pelvic floor (Petersén and Stener, 1970) during ejaculation. Later investigations in patients produced recordings from the bulbocavernosus muscle (Bergman *et al.*, 1979).

It is not thought likely that participation of the 2 muscles in the process of erection in man is essential (Kiss, 1921; Bors and Comar, 1960; Rivard, 1982). Evidence for their involvement relies mainly on recordings of the electrical activity of the muscles during nocturnal penile tumescence (NPT) using surface electrodes (Karacan *et al.*, 1983, 1987; Lavoisier *et al.*, 1988), although one subject in

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another study showed an increase in BC electromyographic activity during erection (Metz, 1986).

Simultaneous registration of the volume of the spurts of semen and the contractile activity of the BC and IC muscles during ejaculation was undertaken in the present study. Since the subjects had first to achieve erection, the opportunity was taken to examine the activity of the muscles during erection induced by visual sex stimulation. A brief account of the ejaculation study was reported to the Physiological Society (Gerstenberg *et al.*, 1987).

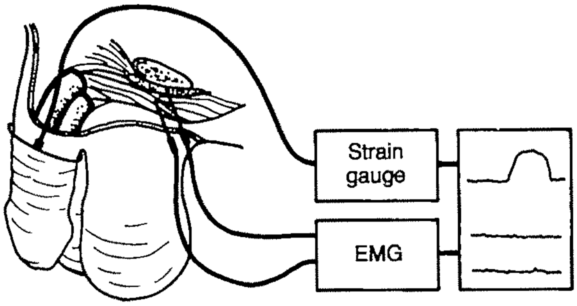

Fig. 1 Diagrammatic representation of experimental simultaneous recording of penile circumference by strain gauge and the EMG activity of the bulbocavernosus and ischiocavernosus muscles on chart recorder.

Materials and Methods

The subjects were healthy, young male volunteers (aged 20–28 years) who answered an advert for experimental subjects placed in the local medical students' magazine. Informed consent was obtained and the Helsinki declaration followed. The BC and IC muscles were located by palpation in the perineum and concentric EMG needle electrodes (0.45 mm diameter, type 13K53, Dantec, Denmark) were inserted into the body of the muscles. The subjects were grounded using a large surface electrode (Indifferent plate, SW-IP 2709, Simonsen & Weel, Denmark) coated with electrode jelly (SW electrode paste) and stuck on the inner thigh. The signals were fed into a 2-channel isolation EMG amplifier (Dantec type 15C01) with signal cut-off settings of 50 Hz (lower limit) and 5 KHz (upper limit). These were then displayed on twin-channel Brush recorders. To check that the electrodes were recording and in the correct position, the subjects were asked to contract their pelvic muscles (as if to stop their flow of urine at urination). All subjects then showed a continuous burst of EMG activity from the muscles. Their EMG activity was recorded during a tumescence/erection/detumescence cycle with the penile circumference monitored by a mercury strain gauge fitted 1 cm from the base of the penis (Fig. 1). Erection was provoked by exposing the subjects to visual sex stimulation (VSS) using commercial, sexually explicit, video tapes. The EMG activity during stimulation to ejaculation was similarly recorded, the subjects viewing the video and either self-stimulating by hand or with the aid of a vibrator. The expulsion of semen was registered by collection in an aluminium pan (20 × 13 × 4 cm) suspended by wire from a sensitive strain gauge (Grass force displacement transducer, model FT03C), the amplified output of which was displayed on a twin-channel Brush chart recorder (Fig. 2). The pan and strain gauge were calibrated by adding known volumes of saline. A thin metal spike was inserted up through the floor of the pan to reduce movement artefact and bounce. The subjects were asked to indicate when they felt their orgasm starting and when it ended.

The EMG activity of the IC and BC muscles was recorded together with the penile circumference in 7 subjects while they were watching sexually explicit videos. All subjects were carefully briefed to make certain that they did not voluntarily contract their pelvic muscles to aid or enhance the erection. We found this briefing essential as one unbriefed subject contracted his pelvic muscles to enhance his arousal.

Results

Electrical activity of the IC and BC muscles during erection and detumescence

A typical result is shown in Figure 3. There was no maintained or burst activity in either the IC or the BC muscles during the tumescent phase and even at full erection (angle of the penis to the body observed to be equal to or greater than 90°) no activity was seen. Rapid detumescence, induced by application of an ice bag to the inner thigh, did not cause any change in electrical activity of either the IC or the BC muscle. In order to check the position of the EMG needles before and after the erection/detumescence cycle, the subject was asked to contract the pelvic muscles. A short burst of EMG activity indicated correct positioning of the electrodes (Fig. 3). An identical result to this was obtained from the other 5 subjects. In the seventh subject, a single motor unit of the BC muscle fired at the peak of the erection.

Electrical activity of the IC and BC muscles during ejaculation

A typical recording of the electrical activity of the

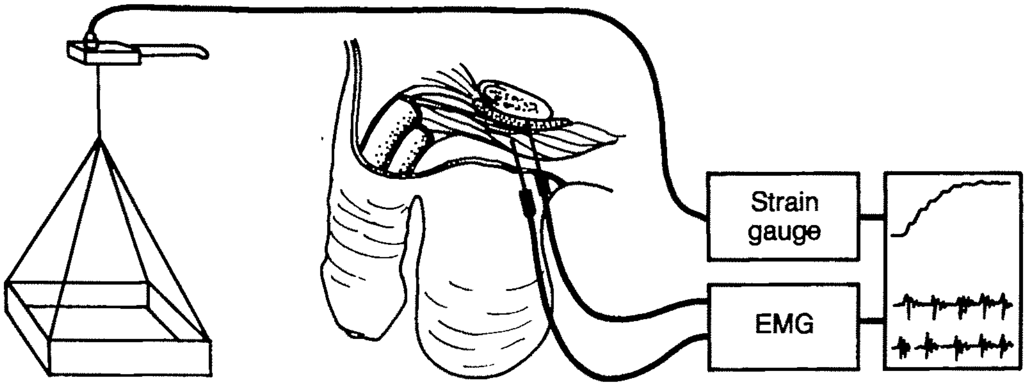

Fig. 2 Diagrammatic representation of simultaneous recordings of ejaculate volume spurts using a pan suspended on a strain gauge and EMG activity of the bulbocavernosus and ischiocavernosus muscles on a chart recorder.

BC and IC muscles during masturbation to ejaculation is shown in Figure 4. The initiation of orgasm, as reported by the subject (s, Fig. 4) occurs clearly before the initiation of the EMG bursts of activity from the BC, but there was a large activity burst from the IC muscle. Fifteen simultaneous bursts of EMG activity occurred in the BC and IC muscles during orgasm. As the orgasm/ejaculation proceeded, the intervals between the EMG bursts increased. The muscle EMG activity ended abruptly, before the reported end of the orgasm (e, Fig. 4). Registration of the EMG activity from voluntary contractions of the BC and IC muscles after ejaculation confirmed that the recording needles were still in position. The activity of the BC muscle during ejaculation with simultaneous recording of the volumes of individual spurts of semen is shown in Figure 5. The record shows that the first burst of BC EMG activity was not accompanied by any increase in the weight of the pan, *i.e.* no semen was ejaculated. Subsequent bursts of EMG activity correlated with an ejaculated spurt of semen. This continued for some 10 EMG bursts. No further expulsion of semen was observed for the last 3 or 4 EMG bursts. Another simultaneous recording of the bursts of EMG activity of the BC muscles with the change in pan weight in a different subject is shown in Figure 6. Again a clear EMG burst of the BC muscle occurred without any semen being propelled on to the pan. The next EMG burst, however, caused a significant increase in pan weight. This subject was unable to report the beginning and end of his orgasm. As his ejaculation proceeded, the characteristics of the EMG bursts changed significantly. Their amplitude decreased and their duration increased together, as did the interburst periods. A significant number of the EMG bursts were not accompanied by any ejaculated semen spurts (approximately 14). The characteristic of the EMG activity at the end of the ejaculation series gradually changed to a continuous "tonic" firing pattern, indicating a muscular tone for about 30 s. A voluntary contraction, some 30 s after the BC muscle became electrically quiescent, showed that the recording needle was still in position.

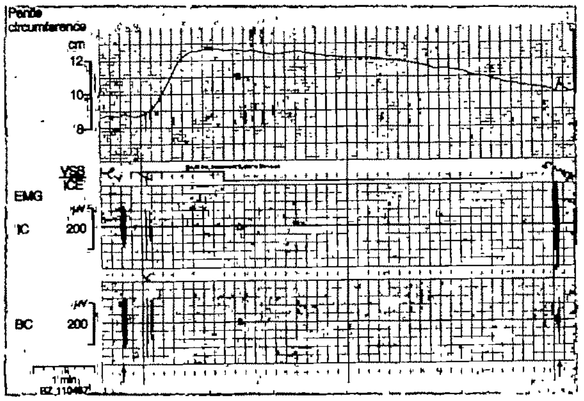

Fig. 3 Record of penile circumference (upper trace) and the EMG activity from the ischiocavernosus (IC, middle trace) and the bulbocavernosus (BC, bottom trace) muscles during a tumescence/detumescence cycle induced by visual sex stimulation (VSS). The duration of the VSS is shown in the upper trace during the first minute followed by the application of the ice pack to the inner thigh to induce rapid detumescence. The arrows at the beginning and end of the cycle denote the EMG activity when the subject was asked voluntarily to contract the BC/IC muscles.

Analysis of the number of contractions of the BC muscle (based on the counted bursts of EMG activity) related to the expulsion of semen and the cumulative percentage of semen expelled at each EMG burst for the 7 subjects are shown in Table 1. In 5 of the 7 ejaculations semen was not expelled at

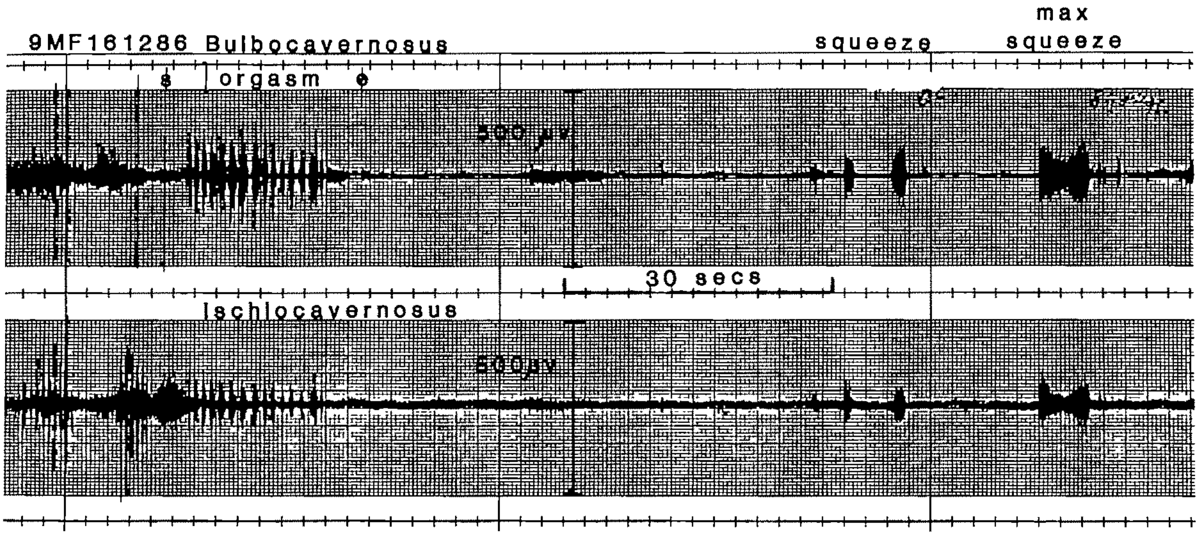

Fig. 4 Simultaneous record of the burst of EMG activity in the bulbocavernosus (upper trace) and ischiocavernosus muscles (lower trace) at ejaculation. Start (s) and end (e) of the orgasm as reported by the subject are shown on the trace. Two voluntary contractions of the muscles are shown (squeeze) and the single maximum contraction (max squeeze).

the first EMG burst but was ejected at the second. Only a limited number of the BC contractions appeared to be needed to eject all of the semen. The range was from a minimum of 26% of the total to a maximum of 60%. Thus even at the maximum, some 40% of the BC contractions were superfluous to semen expulsion. The absolute range of the total number of BC contractions extended from 11 to 33 (mean 19 ± 8 SD, n = 7). The absolute range of the contractions which expelled semen extended from 5 to 10 (mean 7 ± 2, n = 7). Most of the semen volume was expelled after 5 or 6 contractions of the

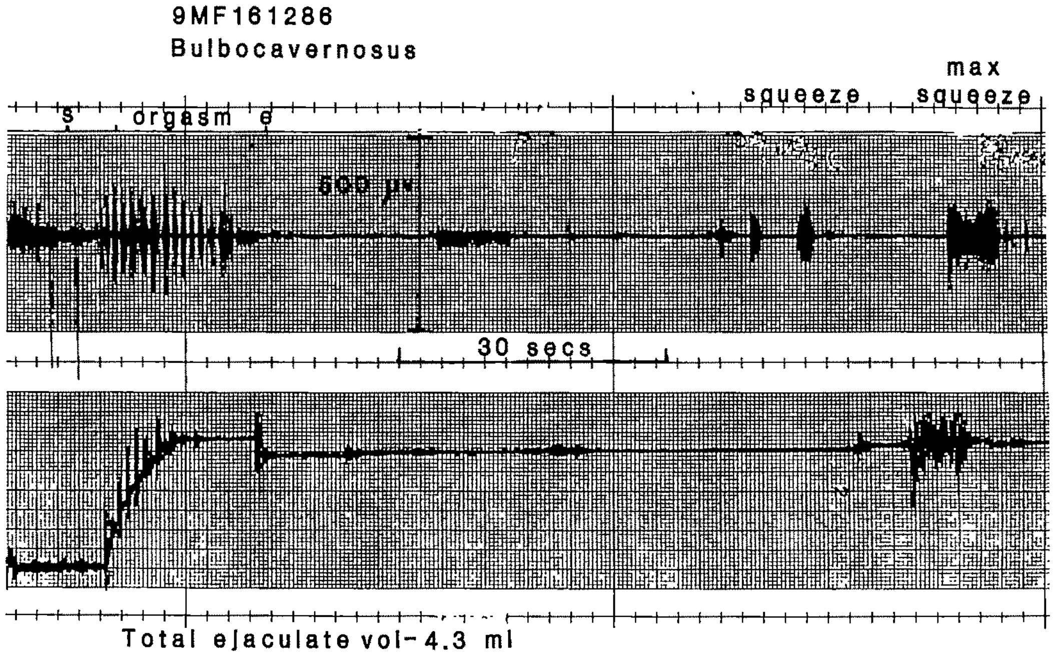

Fig. 5 Record of bursts of EMG activity of the bulbocavernosus muscle (upper trace) with the individual ejaculate semen spurts recording on a pan suspended from a strain gauge. The start and end of the orgasm as reported by the subject is marked with s and e respectively. Two voluntary contractions of the BC muscle are shown (squeeze) followed by a maximum contraction (max squeeze). The recording from the strain gauge shows a movement artefact at e when the subject accidentally moved the suspended pan. Total ejaculate volume was 4.3 ml. The record is from the same subject as in Figure 4.

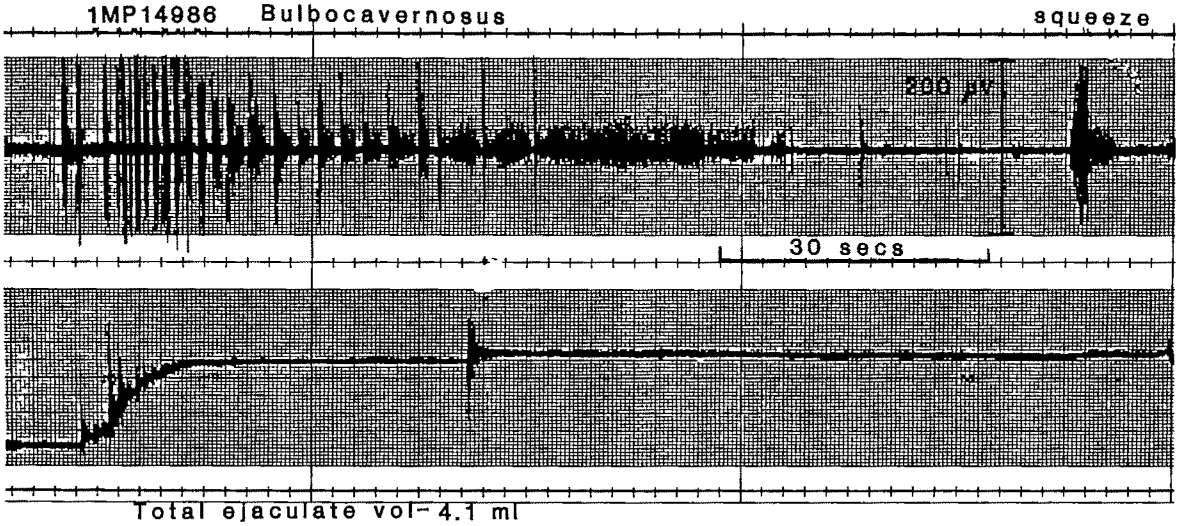

Fig. 6 Record of bursts of EMG activity of the bulbocavernosus muscle (upper trace) with the individual ejaculate semen spurts recording on a pan suspended from a strain gauge (lower trace). A voluntary contraction of the muscle is shown (squeeze). The lower trace has a movement artefact approximately 45 s after the semen spurts when the subject hit the suspended pan.

BC muscle and although the number of subjects was small, it appears that the larger volumes of expelled semen were accompanied by a greater number of expulsive contractions.

Electrical activity of the BC muscle during ejaculation after phenoxybenzamine

Two subjects had their BC EMG activity and volume of semen expelled recorded before (control) and after oral phenoxybenzamine (10 mg doses 18, 10 and 4 h prior to the second ejaculation) 24 h later. The results are shown in Table 2. In the first subject, 9 of the 15 BC EMG bursts (60%) were correlated with semen expulsion (4.2 ml) but no semen was expelled after the phenoxybenzamine, despite there being 12 BC EMG bursts. The subject reported that his subjective orgasm was not different from that of the control 24 h earlier. With subject 2, 11 of the 24 EMG bursts of the BC muscles (46%) were correlated with semen expulsion (3.1 ml). After phenoxybenzamine, 7 of the 22 EMG BC bursts were correlated with semen expulsion of a significantly reduced volume (2 ml). The subject reported that the orgasm was no different from that obtained in the previous control ejaculation.

Discussion

IC and BC activity during erection

The direct EMG recordings of the IC and BC muscles in 7 subjects showed that neither muscle displayed evidence of electrical discharges indicating contractile activity either during the tumescent phase or during full erection. The pioneering studies of Kollberg *et al.* (1962) on the electromyog-

Table 1 Total Number of BC Contractions (Expulsive and Non-expulsive), Total and Cumulative Semen Volume Ejaculated with each Expulsive Contraction

Subject	*Total*	*Expulsive*	*Non-expulsive*	*% expulsive*	*Total semen vol. (ml)*	*Cumulative % semen volume expelled with each contraction*										
						1	2	3	4	5	6	7	8	9	10	11
4	26	8	18	31	4.1	0	20	44	61	78	88	93	96	100	—	—
5	33	10	23	30	4.9	0	16	33	47	63	74	88	92	96	98	100
6	11	6	5	55	3.2	41	55	67	76	88	100	—	—	—	—	—
7	18	6	12	33	3.4	19	54	68	81	92	100	—	—	—	—	—
8	18	5	13	26	2.9	0	43	61	78	92	100	—	—	—	—	—
9	14	5	9	36	1.4	0	30	50	70	90	100	—	—	—	—	—
10	15	9	6	60	4.2	0	19	34	47	59	68	79	92	100	—	—

Table 2 Total Number of BC Contractions (Expulsive and Non-expulsive) and Total Semen Volume Ejaculated in 2 Subjects before and after Phenoxybenzamine (10 mg orally 18, 10 and 4 h before Ejaculation)

Subject		*Total BC*	*BC expulsive*	*% expulsive*	*Ejaculate vol. (ml)*
1	Control	15	9	60	4.2
1	Phenoxybenzamine	12	0	0	0
2	Control	24	11	46	3.1
2	Phenoxybenzamine	22	7	32	2.0

raphy of the striated pelvic musculature during arousal to ejaculation by masturbation showed 2 brief recordings of the BC muscle during ejaculation but none during erection. However, they reported that erection in their subjects could occur without the participation of the pelvic striated muscles they studied, described as "probably" the deep transverse perineal muscle and the BC. In a single recording of BC EMG activity from one subject exposed to visual sex stimulation, Metz (1986) showed that during the 150 s of tumescence/erection, approximately 5 separate bursts of BC activity were each correlated with significant increases in penile circumference. It was not stated whether the subject was briefed specifically to avoid tensing his pelvic muscles during visual sex stimulation to augment the tumescent/erectile process. Our experience shows how critical this is. Other workers (Karacan *et al.*, 1983, 1987; Lavoisier *et al.*, 1988) registered the activity of the muscles by application of surface electrodes to the perineal skin; they recorded NPT erections without monitoring and comparing the signals that these electrodes picked up during erection in the subject when awake. Their recordings have been interpreted as increased electrical activity of the IC and BC muscles during tumescence and erection. Monitoring specific muscles from perineal surface electrodes, however, is unsatisfactory because of the specific large area over which the surface electrodes can pick up signals. The activity may thus come from muscles other than the IC and BC, as it is known that striated muscles may be activated involuntarily during the REM phases of sleep. It may also be assumed that sleep erections and naturally occurring erections when awake are not mediated through the same neural pathways.

While our data show that there is no essential requirement for involvement of the IC and BC muscles to initiate or maintain an erection, there is experimental evidence that the muscles can be used to enhance or augment the rigidity of an already fully tumescent penis. Contraction of the IC muscle (Lavoisier *et al.*, 1986) and voluntary contractions of the pelvic striated muscles greatly enhanced the intracavernosal pressure (Michal *et al.*, 1983; Lue and Tanagho, 1983).

IC and BC muscle activity during ejaculation

The data show that both muscles have a phase where their synchronous bursts of EMG activity correlate individually with the expulsion of a spurt of semen. However, even when all of the semen had been expelled, the muscles still showed synchronous EMG discharges. On the assumption that each burst of EMG activity represented a contraction, it is obvious that the muscles have a phase of expulsive contractile activity during which the semen is expelled but even when this has been accomplished the contractions continue extensively. In the 7 subjects, the "expulsive phase" activity represented between 26 and 64% of the total of such activity. Thus in some subjects, nearly two-thirds of the contractions of the BC muscle were superfluous for semen expulsion. A possible explanation for this is the "safety factor" concept. Because delivery of semen into the female is essential for continuation of the species, many more BC contractions than necessary would always ensure a complete delivery of all sperm into the vagina.

After the phasic bursts at ejaculation, the BC muscle often displayed a short period of tonic activity. This may represent a sustained contraction of the muscle to ensure that the last remains of the semen are squeezed out. The EMG bursts of BC activity were associated with the subjective experience of orgasm but did not appear to correspond exactly to it. The reporting of orgasm can be before the BC activity is expressed (Fig. 4). Similar findings were described by Bohlen *et al.* (1980) when recording anal contractions during ejaculation.

In most of the subjects (5/7) the initial contraction of the BC muscle did not appear to correlate with the first, specific spurt of semen. It was the second and then a number of subsequent contractions that were associated with semen spurts.

The mechanistic correlations between the emission phase, where the various components of seminal fluid are evacuated into the prostatic urethra, the contraction of the prostatic urethra pushing the semen further along and the initiation of the ejaculation phase, where the distal (external) sphincter and the striated muscles of the pelvic area aid in the forceful ejection of semen, have not been closely investigated. Details of the type of semen expulsion observed when only the smooth muscle contractions of accessory organs and of the urethra occur, without the aid of the pelvic muscles, can be found in descriptions of clinical cases (Bors and Comarr, 1960; Kothari, 1984; Brindley, 1985). If the striated muscles do not contract, or contract very weakly, it is claimed that ejaculation is of the dribbling type.

The BC and IC muscles are activated from the brain and/or the thoraco-lumbar and sacral centres of the spinal cord. A possible lack of semen expulsion by the first contraction could be due to a temporal delay between the filling of the upper part of the prostatic urethra and the initial contraction. Not until the prostatic urethra closes off and the distal sphincter opens to allow the seminal fluid to flow into the bulbous urethra is this area primed to be emptied by contractions of the surrounding striated muscles.

The trigger for contraction of the IC and BC muscles

The major experimental evidence against the involvement of semen volume specifically initiating the striated muscle contractions is that subjects taking adrenergic blockers have striated muscle contractions with orgasm but little or no ejaculate is produced because the emission phase is blocked (Money and Yankowitz, 1967; Brindley, 1985). Our 2 subjects who were given phenoxybenzamine were both able to stimulate themselves to orgasm and the BC muscles fired off in their normal clonic pattern. No semen was ejaculated in 1 of the subjects while the other had at least 3 contractions of the BC muscle before the reduced semen volume was ejaculated on to the pan. Both subjects reported that their orgasms felt normal and were apparently uninfluenced by the adrenergic blocker. It is unlikely that the trigger for the initiation of the BC muscle contractions is dependent on a critical volume distension by the semen of any internal organs. All we can postulate is that central/spinal ejaculation centres activate the contractions when they reach a critical firing level.

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PAEDIATRIC UROLOGY

Fetal Vesicoureteric Reflux

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Summary—We present an analysis of 30 patients with fetal vesicoureteric reflux (VUR) from a series of 107 patients with prenatally diagnosed urinary tract anomalies. In 13 patients (Group I) the fetal VUR was the only urinary tract abnormality. In 17 patients (Group 2) the fetal VUR was combined with other urinary tract problems. In 14 of 46 refluxing renal units there was no evidence of upper tract dilatation on a pre- and post-natal ultrasound examination. Any infant with postnatal urinary tract dilatation needs full urological investigations, including a micturating cystogram. A normal postnatal ultrasound examination does not exclude fetal VUR.

One of the less common causes of prenatal hydronephrosis is fetal vesicoureteric reflux (Turnock and Shawis, 1984; Thomas *et al.*, 1985; Smith *et al.*, 1987; Scott and Renwick, 1988). In such infants it should be possible to confirm the diagnosis before the possibility of renal damage from a postnatal urinary infection. It has been suggested that ultrasonography of the renal tract could be used as a screening investigation in children presenting with a urinary infection (Johnson *et al.*, 1986; Lindsell and Moncrief, 1986). It has been common practice to withhold investigations in infants with prenatally diagnosed hydronephrosis provided postnatal ultrasonography showed resolution of the upper tract dilatation. Our experience since 1983 in the management of infants with prenatally diagnosed urinary tract anomalies conflicts with this view. It has been our policy to include a micturating cystogram in the majority of infants with abnormal pre- and post-natal scans. We have reviewed our results to see if this policy is justified.

Patients and Methods

Since 1983, 107 patients with prenatally diagnosed urinary tract anomalies have been studied. The findings were observed during routine obstetric ultrasonography and at least one of these examinations was carried out between 28 and 39 weeks of gestation. All were subjected to postnatal ultrasonography at 3 to 7 days of life and in the majority a second or third examination was performed; 97 patients had a micturating cystogram. Other investigations included intravenous urography, isotopic renography and cystoscopy.

There were 182 urological anomalies in the 107 patients; 30 had VUR (46 renal units). These 30 patients (18 males, 12 females) formed the study group. Patients with VUR secondary to a neurogenic bladder and posterior urethral valves were excluded. The 30 patients were subdivided into 2 groups: in Group I the VUR was the only abnormality (13 patients) and in Group II (17 patients) the VUR was associated with other congenital anomalies of the urinary tract.

Results

Group I (13 patients: 24 renal units) (Table 1)

These patients had a micturating cystogram between 3 days and 23 weeks after delivery. (mean 7 weeks). The VUR was bilateral in 11 and unilateral in 2 patients (Rt 1, Lt 1) and was usually severe, with grades III and IV accounting for 21 renal units (grade IV 15, grade III 6, grade II 1 and grade I 2). In all of these patients ultrasonography had demonstrated upper tract dilatation before and after

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delivery, but in 4 patients (Nos 5, 6, 7 and 8) with VUR of varying grades (I–IV), dilatation of individual renal units was not seen. In patient 9 the upper tract dilatation was noticed on a prenatal ultrasound scan at the time of bladder emptying, thus suggesting fetal VUR.

Group II (17 patients: 22 renal units) (Table 2)

These patients had a micturating cystogram between 4 days and 6 weeks after delivery (mean 3 weeks). The VUR was bilateral in 5 and unilateral in 12 (Rt 7, Lt 5). The associated anomalies ranged from multicystic kidney (4), pelviureteric junction (PUJ) hydronephrosis (3), megaureters (3), double ureters (1), ectopic ureter to seminal vesicle (1) and renal agenesis (1). All of these patients were fully investigated because of the dilatation associated with the urinary tract anomalies. In 10 patients (Nos 14, 16, 17, 18, 19, 20, 21, 22, 23 and 24) there was VUR on the contralateral side varying in grades from I to IV without evidence of upper tract dilatation on prenatal ultrasonography.

Table 1 Group I. Patients with Vesicoureteric Reflux and no other Urinary Tract Abnormalities

Patient no.	*Prenatal ultrasound dilatation*		*Postnatal ultrasound dilatation*		*Grade of VUR*	
	Rt	*Lt*	*Rt*	*Lt*	*Rt*	*Lt*
1	+	+	+	+	IV	IV
2	+	+	+	+	IV	IV
3	+	+	+	+	IV	IV
4	+	+	+	+	III	IV
5	–	+	–	+	IV	III
6	+	–	+	–	IV	III
7	+	–	+	–	II	I
8	+	–	+	–	III	I
9	+	+	+	+	III	IV
10	+	+	+	+	IV	IV
11	+	–	+	–	III	
12	–	+	–	+		III
13	+	+	+	+	IV	IV

Table 2 Group II. Patients with Vesicoureteric Reflux Associated with other Urinary Tract Abnormalities

Patient no.	*Prenatal ultrasound dilatation*		*Postnatal ultrasound dilatation*		*Grade of VUR*		*Other urinary tract abnormalities*
	Rt	*Lt*	*Rt*	*Lt*	*Rt*	*Lt*	
14	–	+	–	+	IV		Multicystic kidney (Lt)
15	–	+	–	+		I	PUJ hydronephrosis (Lt)
16	+	–	+	–	I	I	Multicystic kidney (Rt)
17	–	+	–	+	II		Multicystic kidney (Lt)
18	–	+	–	+	IV		Multicystic kidney (Lt)
19	–	–	–	–		I	Renal agenesis (Rt)
20	–	+	–	+	II	III	Double ureters + ureterocele (Lt)
21	–	+	–	+	III	IV	Double ureters + ureterocele (Lt)
22	–	+	–	+	I	III	PUJ hydronephrosis (Lt)
23	–	+	–	+	III	IV	Megaureter (LT)
24	–	+	–	+	II		PUJ hydronephrosis (Lt)
25	+	+	+	+	IV		Megaureters (bilat)
26	–	+	–	+		III	Double ureters + ureterocele (Lt)
27	–	+	–	+		II	Double ureters + ureterocele (Lt)
28	–	+	–	+		IV	Megaureter (Lt)
29	+	–	+	–	IV		Double ureters (Rt)
30	+	–	+	–	I		Ectopic ureter to seminal vesicle

Discussion

In this series of 107 patients with prenatally diagnosed urinary tract anomalies, fetal VUR was found in 30 cases (28%). Other investigators have reported a lower incidence (Gunn *et al.*, 1988; Watson *et al.*, 1988). This discrepancy is almost certainly due to the number of micturating cystograms performed (in 25% of patients by Gunn *et al.* (1988) and in 67% by Watson *et al.* (1988)). This contrasts with our own series, in which 97 patients (90%) had a micturating cystogram.

In Group I the fetal VUR was sufficiently severe to cause upper tract dilatation on pre- and postnatal ultrasound examinations. However, right Grade IV VUR was seen in patient No. 5, in whom there was no upper tract dilatation before or after birth. Similarly, in Group II patients Nos 14 and 18 had Grade IV VUR without evidence of upper tract dilatation before or after birth. Thus in the combined series a total of 14 patients (47%), or 14 of 46 refluxing renal units (30%), had fetal VUR without evidence of upper tract dilatation.

It seems likely that patients with fetal VUR will not necessarily be diagnosed prenatally. However, in this series the diagnosis was established following full urological investigation of infants in whom upper tract dilatation was found on pre- and postnatal ultrasonography. We know that there are infants within our region in whom prenatal dilatation had been noted but who were not referred for full investigation because the renal tract was found to be normal on a postnatal scan. It seems likely that some of these infants will have VUR and they may present at a later date with urinary infection.

It is therefore tempting to recommend a micturating cystogram on all infants shown to have upper tract dilatation on a prenatal scan. One of the difficulties with this recommendation is that there is no agreement about the parameters which constitute hydronephrosis of the fetal kidney. In one series, prenatally determined upper tract dilatation was as high as 8% (Gunn *et al.*, 1988). It seems inadvisable to perform invasive investigations such as a micturating cystogram in all such patients.

The sequel of this is that the diagnosis of fetal VUR will not always be confirmed in the neonatal period. We therefore suggest that micturating cystography is indicated in all infants with an abnormal pre- and post-natal ultrasound examination of the renal tract. In patients with a normal postnatal ultrasound scan, close supervision is required for some years with routine urine examinations to exclude infection. Therefore the possi-

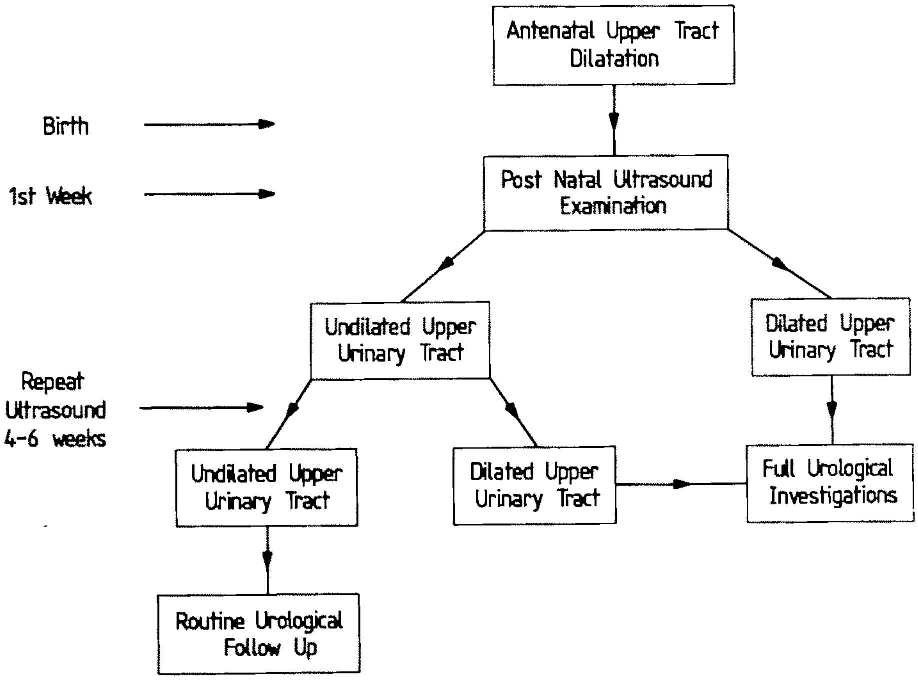
Antenatal Upper Tract Dilatation
Birth
1st Week
Post Natal Ultrasound Examination
Undilated Upper Urinary Tract
Dilated Upper Urinary Tract
Repeat Ultrasound 4-6 weeks
Undilated Upper Urinary Tract
Dilated Upper Urinary Tract
Full Urological Investigations
Routine Urological Follow Up

Fig. Plan of management of upper urinary tract dilatation found on prenatal ultrasonography.

bility remains that there may be urinary tract problems in the future. The concept that a normal postnatal ultrasound scan excludes significant urinary tract pathology should be abandoned. A suggested plan of management for patients shown to have prenatal upper tract dilatation is seen in the Figure.

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Prenatally Diagnosed Reflux: a Follow-up Study

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Summary—This report analyses the characteristics and outcome of 25 infants with vesicoureteric reflux detected prenatally on the basis of dilatation of the fetal urinary tract. Sixteen infants had bilateral reflux—a total of 41 refluxing units.

The high proportion of males (84%) contrasts with clinically presenting reflux, which is dominated by females. Prenatally diagnosed reflux is generally of a higher grade—usually grade IV.

Eight children (32%) had coexistent congenital abnormalities. Chemoprophylaxis was completely effective in 17 children (68%), who remained infection-free; 3 children (12%) had a single urinary infection and were managed conservatively whilst 5 (20%) experienced 2 or more infections and required reimplantation or vesicostomy. Spontaneous cessation of reflux was observed in 6 (35%) of 17 refluxing ureters reassessed after a mean interval of 2.1 years.

The significance of isotope findings was sometimes difficult to assess but results in 30 refluxing units support the concept that focal renal scarring is usually a consequence of infected reflux in postnatal life.

Dilatation of the fetal urinary tract is being detected with increasing frequency on ultrasound imaging in pregnancy. Whilst this dilatation is most often due to obstructive uropathy (Thomas and Gordon, 1989), it may also result from other mechanisms—particularly vesicoureteric reflux (VUR). The ability of prenatal ultrasound to identify some infants with VUR before birth represents an exciting opportunity to study the natural history of reflux and the aetiology of reflux nephropathy. It is also possible that this prenatal diagnosis may be of benefit to affected individuals by reducing the morbidity associated with urinary infection and renal scarring.

The study was undertaken with 3 broad aims:

1. To establish the characteristics of infants with prenatally diagnosed reflux.
2. To document the post-natal clinical course of this condition.
3. To investigate the possibility that the prenatal diagnosis of vesicoureteric reflux might shed new light on mechanisms of renal scarring and reflux nephropathy.

Patients and Methods

The study covered a 5-year period from July 1983 to June 1988. During this time 25 infants with primary VUR detected prenatally were managed by the Regional Paediatric Urological Service in Leeds. Infants with reflux secondary to urethral valves or neuropathic bladder were excluded from the series, but it did include 2 infants with duplex systems.

All of the infants were initially assessed by ultrasound during the first few days of life. This was followed by a micturating cystogram (performed under antibiotic cover) in cases where ultrasound had confirmed the presence of dilatation. The single exception was an infant in whom dilatation had been detected prenatally but whose initial postnatal ultrasound appeared normal. An MCU was not, therefore, performed and antibiotic prophylaxis was not initiated. He developed a urinary infection at 6 months of age and at this

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stage a micturating cystogram was performed which demonstrated bilateral vesicoureteric reflux. Since is is almost certain that this infant did have VUR *in utero*, he has been included in the series. Isotope imaging usually consisted of a ^{99}Tc dimercaptosuccinic acid renogram (DMSA scan) at approximately 1 month of age. Cystoscopy was not performed routinely. Infants with documented reflux were managed on continuous antibiotic prophylaxis—usually trimethoprim 1–2 mg/kg/day. This was combined with regular urine microscopy and culture.

The study comprised a retrospective review of the earlier patients and also an analysis of information derived prospectively from the following protocol:

Ultrasound: day 1 to 3 (repeated if normal).
Micturating cystogram: day 1 to 3.
DMSA scan: 4 to 6 weeks.
Ultrasound scan: 1 year.
DMSA scan: 2 years.
Micturating cystogram: 2 years.

Results

Characteristics

Of the 25 affected infants, 16 had bilateral reflux; thus 41 refluxing ureters were studied. The series included 21 males (84%) and 4 females (16%), a male to female sex ratio of 5:1.

Reflux was graded on a scale of I to V according to the classification devised by the International Reflux Study Committee (1981). All 5 grades of reflux were detected, but the emphasis was on the higher grades, grade IV being encountered with the greatest frequency (Table 1). Grades of reflux which are not associated with dilatation (I and II) were occasionally detected in their own right, but were more commonly identified during the investigation of higher grade reflux in the contralateral ureter.

Eight infants (32%) had other congenital abnormalities (Table 2). In 5 infants these anomalies were confined to the urinary tract. In 3 cases, however, reflux represented only 1 part of a severe multisystem disorder. Two of these children died and in both cases the cause of death was unrelated to the VUR.

Table 1 Distribution of Grades of Reflux

Grade	*No. of units*	*%*
1	3	7.3
2	5	12.2
3	10	24.4
4	13	31.7
5	10	24.4

Table 2 Associated Congenital Abnormalities

Urological
Contralateral renal agenesis
Bilateral pelviureteric junction obstruction
Contralateral multicystic dysplastic kidney
Ipsilateral duplex system
Contralateral duplex system

Non-urological
Robinow syndrome
Hydrocephalus/multiple abnormalities
Dysmorphism

Clinical Course

Morbidity in this group of infants with prenatally diagnosed reflux was related almost entirely to urinary infection: 8 children (32%) developed urinary infection despite continuous antibiotic prophylaxis. In 3 of these patients, however, the infection was confined to a single episode and sterile urine has subsequently been maintained with antibiotic prophylaxis. Five children (8 ureters) have been managed surgically. In 3 children (5 ureters) the surgery consisted of reimplantation, which was universally successful in correcting the reflux and controlling infection. In addition, 2 infants (1 with bilateral reflux and 1 with reflux into a solitary kidney) underwent cutaneous vesicostomy rather than initial reimplantation. The vesicostomies were subsequently closed in the second year of life. Both children have since done well and have not required ureteric reimplantation. Of the 21 male infants in the series, none underwent neonatal circumcision; 7 of them developed urinary infection. The majority of the refluxing units (33/41: 81%) were successfully managed with conservative therapy.

Seventeen refluxing units have been re-evaluated by repeat cystography at a mean interval of 2.1 years (Figs 1 and 2). In approximately one-third of ureters (35%) the reflux ceased completely; in one-third reflux was still present, but at a lower grade, whilst in the remaining third it was unchanged.

Reflux Nephropathy

Not all of the refluxing units were imaged satisfactorily with isotopes. In the earlier part of the series some kidneys were investigated with ^{123}I Hippuran, which in our experience gave less precise images and doubtful information on focal scarring. Fur-

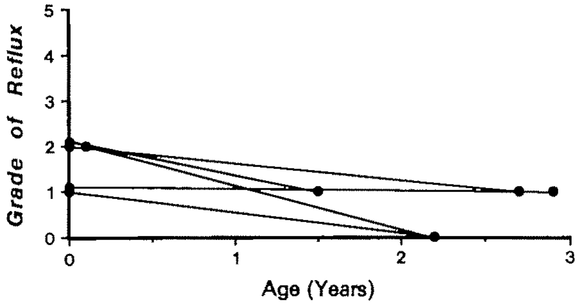

Fig. 1 Results of follow-up of reflux grades 1 and 2. Each line represents one ureter, each point represents the grade of reflux on initial and follow-up cystograms.

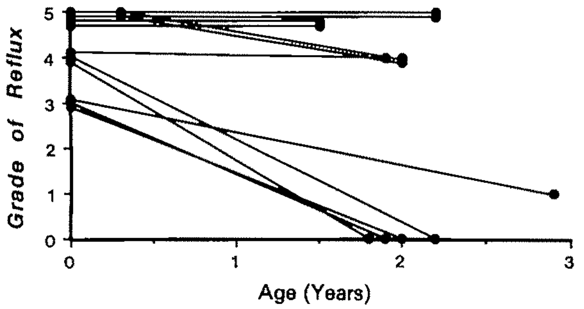

Fig. 2 Results of follow-up of reflux grades 3 to 5.

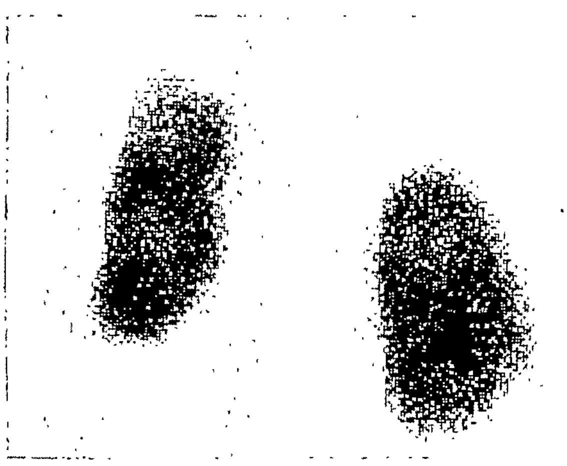

Fig. 3 DMSA scan in an infant who experienced documented urinary infection. Patchy loss of uptake of isotope is consistent with renal scarring (or, possibly, dilated collecting systems).

thermore, isotope evaluation was omitted in some asymptomatic infants with low grade reflux. Thirty kidneys, however, were evaluated using ^{99}Tc DMSA. The findings are summarised in Figure 1. Six kidneys were known to have been exposed to documented urinary infection and all showed evidence of renal impairment—either focal scarring (4 kidneys) (Fig. 3) or reduced uptake of isotope in the absence of focal scarring (2 kidneys). There were 18 kidneys which, to our knowledge, had only been exposed to sterile reflux and which showed no evidence of focal scarring or reduced uptake of isotope. Two solitary kidneys which had not been exposed to infection showed no evidence of scarring, but in the absence of a contralateral kidney it was not possible to calculate differential function.

Finally, there was an interesting group of 4 kidneys which had not, as far as we could ascertain, been exposed to documented infection which showed no focal scarring but which had a reduced proportion of differential function (40, 44, 38 and 40%) (Fig. 4). We have not yet encountered a grossly dysplastic kidney in association with prenatally diagnosed reflux, the lowest figure for differential function being 38%.

Discussion

Vesicoureteric reflux is usually diagnosed when it gives rise to urinary infection. The characteristics of children with clinically presenting reflux are now well documented in the literature. Much less is known about the incidence and significance of asymptomatic reflux in the paediatric population. Studies of siblings have identified a relatively high incidence (32%) of unsuspected reflux in these selected groups (Jerkins and Noe, 1982). In a study of an unselected population of urologically healthy infants, Köllerman and Ludwig (1967) performed routine micturating cystography and found reflux in 30%.

Prenatal ultrasound imaging now offers a non-invasive method of identifying some asymptomatic infants with reflux (mainly higher grades) who would hitherto have remained undiagnosed until the onset of urinary infection. Infants with prenatally diagnosed reflux appear to differ in 3 respects from children who present clinically with reflux: (1) a higher proportion of males, (2) greater severity of reflux and (3) a higher incidence of coexistent anomalies.

The finding of a male to female ratio of 5:1 contrasts with clinically based series, which invariably report a female preponderance. Most large

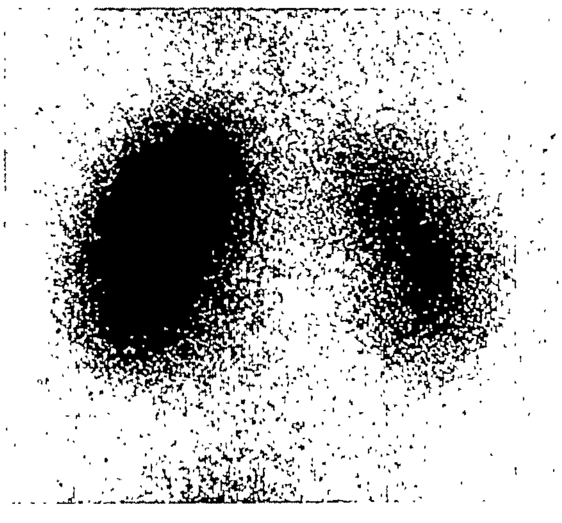

Fig. 4 DMSA scan showing diffuse loss of function in left kidney in an infant with bilateral reflux without documented infection.

studies (Dwoskin and Perlmutter, 1973; Skoog *et al.*, 1987) cite a female to male ratio of 4:1 and 6:1. A possible explanation for this difference is illustrated by Lenaghan *et al.* (1976), who analysed the sex ratio at different ages of presentation. They found that females with reflux dominated the age group from 3 years and upwards—the age range which contributes the largest proportion of patients to most clinically based studies. The high proportion of females in this older group usually outweighs the male preponderance amongst the smaller numbers of children presenting with reflux in the first or second year of life. In these early years, however, reflux is more commonly seen in boys. Lenaghan *et al.* (1976) found that the proportion of males in the first year of life was very similar to that seen in our group of infants with prenatally diagnosed reflux (Fig. 5). Another explanation for the high proportion of males with prenatally diagnosed reflux has been suggested by Scott (1987), who noted that 6 of the 7 reported cases of "fetal reflux" in his series were male. Scott argued that in neonates the true incidence of reflux in males was at least as high as in females, but in the absence of infection, reflux in boys is more likely to go unrecognised.

Prenatal ultrasound imaging has identified infants with higher grades of reflux than those most commonly encountered in symptomatic children. In a large study by Skoog *et al.* (1987) the most frequently observed grade of reflux was grade II, as opposed to grade IV in the prenatally diagnosed group (Fig. 6). It could be argued that this is not an unexpected finding, since ultrasound can only be used to detect dilatation—a feature of higher grade reflux. It is possible that prenatal ultrasound is failing to detect large numbers of fetuses with lower grades of reflux. The only means of establishing the true pick-up rates would be to perform routine cystography on a population of neonates who had previously been screened with prenatal ultrasound.

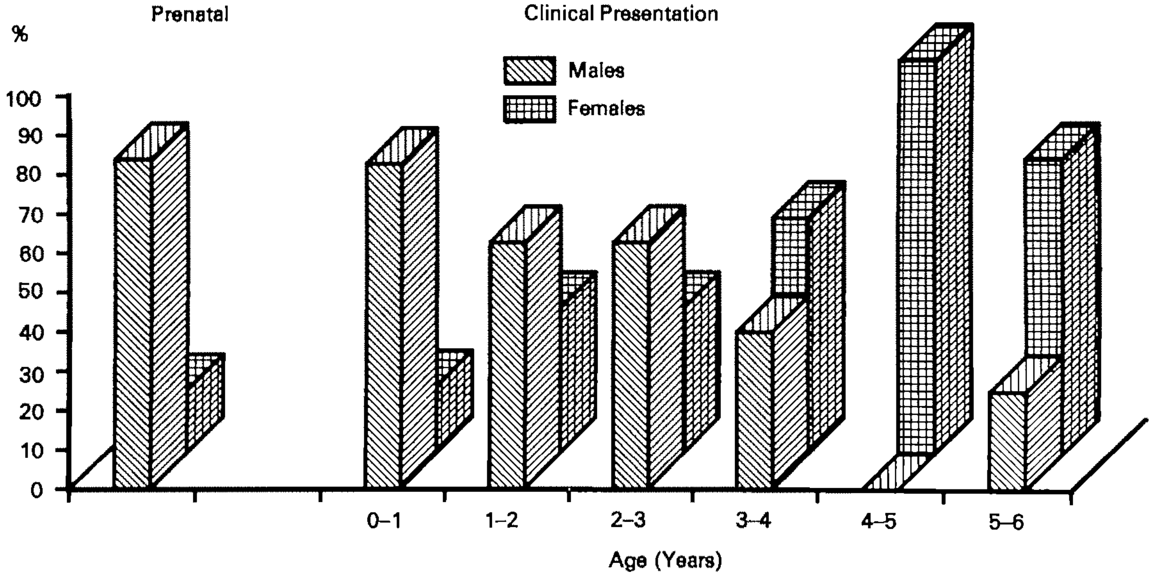

Fig. 5 Comparison of sex incidence between prenatally diagnosed patients (this study) and children with clinically presenting reflux (Lenaghan *et al.*, 1976).

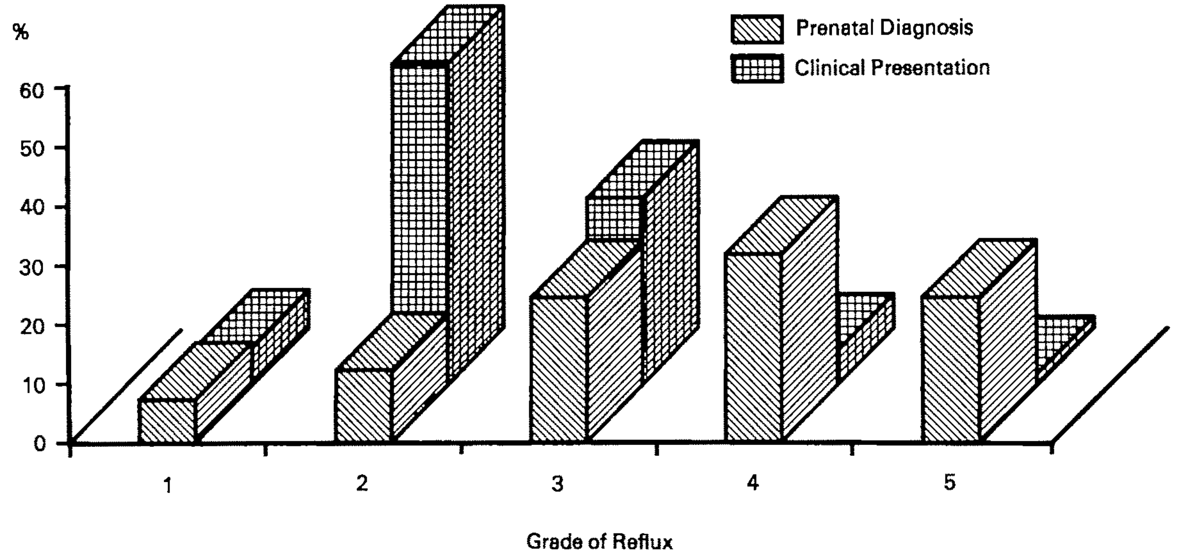

Fig. 6 Percentage of refluxing ureters in each grade of reflux at presentation in prenatally diagnosed reflux (this study) and clinically presenting reflux (Skoog *et al.*, 1987).

In view of the invasive nature of contrast cystography, however, it is doubtful whether such a study could be ethically justified.

It is possible that prenatal ultrasound may be identifying those cases of reflux which are primarily anatomical in origin and which are more common in males. In contrast, clinically presenting reflux is seen more typically in females and is of a lower grade. In this group the reflux may be related more to bladder dysfunction than to a significant congenital abnormality of the vesicoureteric junction. The findings of Deckter *et al.* (1988) in their analysis of boys with reflux tend to support this view. These authors reported that reflux in boys was likely to be of a higher grade than in girls and tended to present earlier in life.

Published studies contain little information on the incidence of congenital anomalies in children presenting with symptomatic vesicoureteric reflux. Clinical experience suggests, however, that the figure is likely to be considerably less than the 32% incidence of other abnormalities encountered in this study.

The relatively high incidence of breakthrough infection in our series (32%) was disappointing, particularly in relation to the 6% infection rate reported by Deckter *et al.* (1988) in their group of young males with reflux. No breakthrough infections were reported in Scott's series of infants with "fetal reflux" (Scott, 1987). Comparable figures for breakthrough infection have, however, been reported for some of the large clinical reflux studies, *e.g.* 29% reported by Edwards *et al.* (1977).

The factors contributing to the urinary infection rate in our patients are not clear. Compliance with antibiotic prophylaxis appeared to be good. None of the infections was precipitated by micturating cystography, although a severe infection did occur in one of the few children who underwent cystoscopy. None of the boys had undergone neonatal circumcision. Although this is unlikely to be of significance in normal males, it is conceivable that the presence of the prepuce may increase the risk of ascending infection in boys with vulnerable refluxing upper tracts. To test this hypothesis we have adopted Ransley's suggestion and set up a randomised prospective trial of circumcision in boys with vesicoureteric reflux.

Although only a limited number of ureters have so far been reinvestigated by cystography, the initial findings are encouraging, *i.e.* spontaneous cessation of reflux in one-third of grades III to V refluxing ureters on follow-up at 2 years. It is likely that the eventual cessation rate for prenatally diagnosed reflux will be at least equal to the spontaneous cessation rate for clinically presenting reflux. It is not clear whether older boys with persisting but asymptomatic reflux and normal bladder function need to remain on antibiotic prophylaxis. The experience of Deckter *et al.* (1988) suggests that the risk of infection in older boys with reflux is low.

Despite the need for surgical intervention in 5 children (20%), we believe that the initial approach to prenatally diagnosed reflux should be conservative. Most of the refluxing units encountered in this study were successfully managed on antibiotic prophylaxis with either no infection or a single infection. Any possible benefits of neonatal ureteric reimplantation must be weighed against the risk of making the situation worse by introducing an element of obstruction. The successful reimplantation of a wide ureter into the small bladder of an infant is technically challenging and gives less predictable results than ureteric reimplantation in later childhood. Surgical alternatives to reimplantation, such as cutaneous vesicostomy (or circumcision?), merit consideration.

Isotopic investigation of renal function and morphology in infants with prenatally diagnosed reflux might yield valuable insight into the mechanisms of renal damage associated with VUR. There is now broad agreement that imaging with ^{99}Tc DMSA is superior to ultrasound or intravenous urography as a means of demonstrating renal scarring in neonates and infants (Monsour *et al.*, 1988). However, Smellie *et al.* (1988) suggested that DMSA may underestimate the incidence of scarring in this age group and they argued the case for retaining intravenous urography to investigate these patients.

Although figures for differential uptake of isotope are computer generated, the initial marking out of areas of interest and the visual interpretation of renal morphology are both subject to potential observer error. Although we are now collecting information derived from isotope imaging on a prospective basis, this study does include some data collected retrospectively. The number of kidneys studied is relatively small. For all of these reasons, therefore, it would be unwise to draw anything other than tenative conclusions from the results of the isotope imaging. Nevertheless, the findings are in broad agreement with the view that renal scarring results principally from the combination of infection and reflux in postnatal life. Focal scarring was seen only in kidneys which had been exposed to proven infection. Furthermore, the majority of kidneys which had not been exposed to infection functioned well and showed no evidence of focal scarring. There was, however, the group of 4 kidneys in which urinary infection had never been documented but which nevertheless showed reduced function (between 20 and 40% of differential uptake) on imaging with DMSA. Were these kidneys damaged by sterile reflux during gestation or in early postnatal life? It is, perhaps, rather surprising that none of the 41 prenatally diagnosed refluxing units was associated with a grossly dysplastic, poorly functioning kidney. This may simply reflect the relatively small size of the series. If, however, this pattern of presentation was maintained in a larger group it would suggest that postnatal infection rather than dysplasia is the major factor in the aetiology of end-stage reflux nephropathy.

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Results of Surgical Treatment of Severe Vesicoureteric Reflux

Retrospective Study of Reflux Grades 4 and 5

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Summary—A series of 80 children underwent surgery in the Sophia Children's Hospital for gross reflux grades 4 and 5. In this retrospective study the success rate for ureteric reimplantation was 90%. Analysis of growth showed that after surgery the children tended to fall within the normal ranges for height and weight. Deterioration in renal function was progressive in 3 children. New renal scars developed in 13% of renal units. Initially non-refluxing kidneys showed no further deterioration. Moderate hypertension was found in only 4 patients.

It was concluded from a prospective study (Scholtmeijer and Griffiths, 1988) that reflux grades 1, 2 and 3 are best treated initially by conservative medical treatment and that surgery should only be performed in the event of troublesome infections or worsening reflux. For gross reflux (grades 4 and 5) no benefit can be expected from this regimen: in 24 renal units with gross reflux surgical treatment was successful in every case. In the conservatively treated group of 12 patients, reflux disappeared in only 3.

The surgical approach is therefore our first choice in the treatment of children with gross reflux.

In this retrospective study we have investigated the results of immediate surgical intervention in the treatment of urinary reflux grades 4 and 5 in children treated between 1972 and 1983.

Patients and Methods

A series of 80 children with urinary reflux grades 4 and 5 was reviewed; 29 male (36%) and 51 female patients (64%) were initially treated for reflux by reimplantation according to the Politano–Leadbetter method. Other, less frequently used techniques were the Cohen procedure and the Lich Gregoir and Hendren operations. The patients were aged between 0 and 15 years of age (Fig. 1). Most presented during the first 3 years of life (55%), with 30% in the first year. The mean age was 3.5 years. All presented with symptoms related to urinary tract infection.

The period of follow-up ranged from 6 months to 13 years (mean 64 months).

Grading of reflux on the voiding cystogram and parenchymal scarring of the kidney on the intravenous urogram was carried out according to the International Reflux Study Committee (1981).

The following factors were reviewed: success of the operation, kidney damage, gain in weight and height relative to the general population, development of hypertension and renal function expressed in terms of serum creatinine and creatinine clearance/1.73 m^2.

Results

Fifty-six kidneys with reflux grade 4 and 50 with reflux grade 5 were treated by 70 single operations. In 10 cases a second operation was performed and 2 patients required surgery on 3 occasions (Table).

The initial success rate was 90%. Repeat surgery was necessary in 10 patients as detailed in the Table. Finally, 101/106 patients (96%) were cured of urinary reflux.

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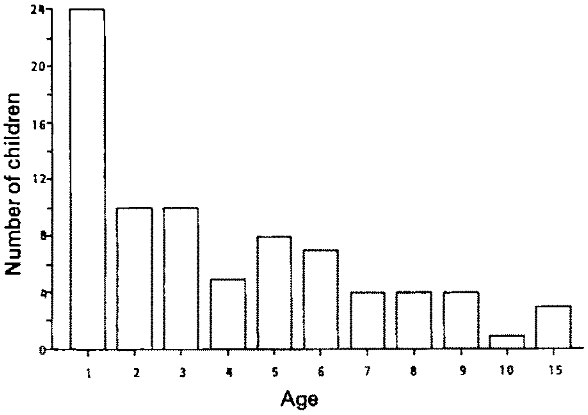

Fig. 1 Age distribution at diagnosis.

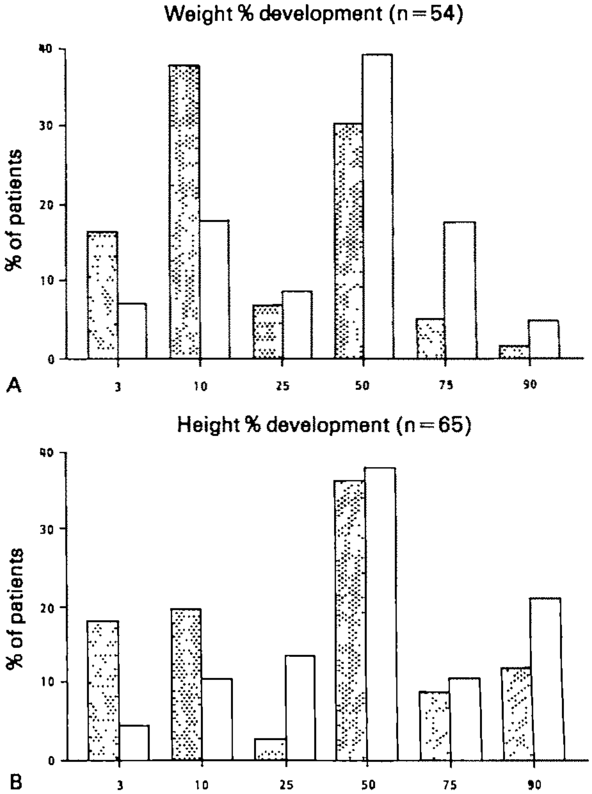

Fig. 2 Development of weight (A) and height (B) during follow-up expressed in terms of normal population distribution. Hatched columns represent pre-operative distribution and blank columns represent distribution during follow-up.

The results showed that body weight tended to be more retarded than height in children with severe reflux. Of 80 children, 54 were checked for weight and 65 for height. None was subjected to medical treatment for a period longer than 2 to 4 weeks before reimplantation; 61% were initially in the lowest weight-age quartile and for the lowest height-age quartile the corresponding figure was 40%. After reflux had been resolved by operation and infection had been treated, weight and height tended to recover to within normal ranges: after treatment only 21% remained in the lowest weight-age quartile and only 19% in the lowest height-age quartile (Fig. 2).

Renal function deteriorated during follow-up in 3 patients. In all others the serum creatine level increased to approximately the normal value for the body mass. In 2 patients, creatinine clearance decreased from 53.7 to 44.9 ml/min/1.73 m^2 and from 96.8 to 72.5 ml/min/1.73 m^2 during 7 and 8 years of follow-up respectively. The first patient had bilateral reflux grade 5 and a scarred kidney grade C; the second had unilateral reflux grade 4 and renal scarring initially grade A on IVU, deteriorating to grade B. One other patient deteriorated more significantly, from 30.1 to 18.4 ml/min/1.73 m^2 during 12 years of follow-up. This patient had bilateral reflux grade 5 with renal scarring grades A and B that developed to grade C on both sides. On presentation at the clinic these patients were 2, 3 and 4 years of age respectively.

Of 80 patients, 71 were checked periodically for blood pressure and 6 were found to have initial hypertension; in 2 patients, 2 and 8 years of age,

Table Reoperations in 10 Patients with Initial Reflux Grade 4 or 5

Reason for reoperation	*No. of patients*	*First reoperation*	*Result*	*Second reoperation*	*Result*
Persistent reflux grade 4	5	Reimplantation	Good (4). Stenosis of previously implanted contralateral ureter (1).	Reimplantation	Good
Coexistent contralateral reflux grades 2 or 3	2	Reimplantation	Good (2)		
Coexsistent contralateral reflux grade 4	1	Reimplantation	Poor (1)	Nephrectomy	
Stenosis of reimplanted contralateral ureter	1	Nephrectomy			
Stenosis of reimplanted ureter	1	Reimplantation	Good (1)		

the diastolic blood pressure was 100 mm Hg: in one 6-year old patient it was 95 mm Hg and in the other 3 patients, aged 4 months, 5 and 8 years, it was 85 to 90 mm Hg.

Two of these children presented with undamaged kidneys on IVU and 3 had unilateral scarring grades A, B and C respectively. One patient showed bilateral scarring grade A.

After treatment, all but a 5-year-old girl regained normal diastolic tension. In correlation with their age, 3 other patients, girls of 4 months, 4 and 7 years of age, developed moderate hypertension after a follow-up of 5 to 12 years. All suffered some unilateral renal damage, grade B in 1 case and grade C in 2. Thus, after treatment, 4/71 patients (5.6%) had a diastolic tension of 85 to 90 mm Hg.

At presentation there were 160 renal units, 54 of which (34%) were already damaged. New renal scars were seen in 23 renal units (13%), predominantly in patients with bilateral reflux (13/21 renal units) while 8/21 came from the unilaterally refluxing group. Of 26 patients with bilateral reflux, 6 showed new scars in both kidneys (23%) and 1 (4%) in a single kidney. In 54 patients with unilateral reflux grades 4 or 5, 8 (14%) showed new scars in the kidney concerned. No kidney without reflux showed new scars.

Of 9 kidneys initially undamaged, 4 developed grade A scarring, 2 grade B or grade D and 1 grade C scarring (Fig. 3).

Kidneys that had already been damaged usually deteriorated by one grade; only 2 grade A kidneys changed to grade C and 1 grade D became silent.

Discussion

The male:female ratio in the present series was 29:51 (36 versus 64%). This is in accordance with other series (Wallace *et al.*, 1978; Carpentier *et al.*, 1982; Quinlan and O'Donnell, 1985).

It has been shown that ureteric reimplantation is a reliable and safe procedure for treatment of urinary reflux grades 4 and 5. As shown here, no serious morbidity occurred, even in cases of gross reflux.

Our success rate is comparable with that of other series (Lyon *et al.*, 1980; International Reflux Study Committee, 1981). Wallace *et al.* (1978) studied 158 patients, of whom 24 needed a second surgical procedure (9 for obstruction, 10 for reflux and the rest for nephrectomy and incontinence). Quinlan and O'Donnell (1985) reported a success rate of 98% in 50 patients with unilateral reflux.

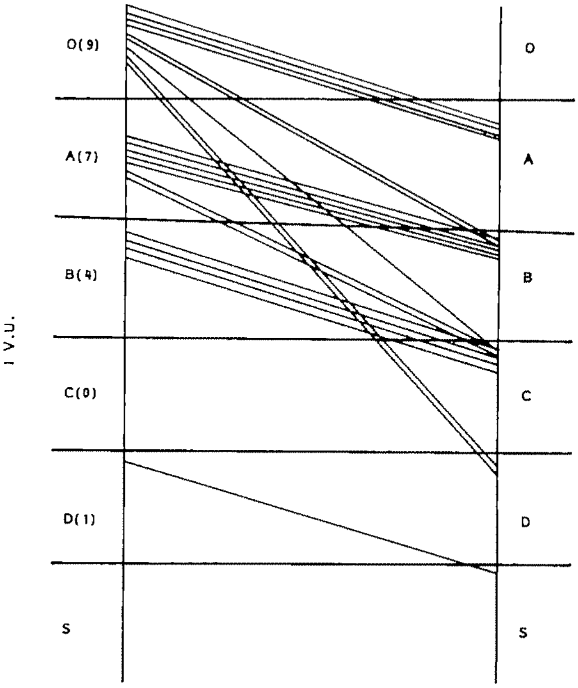

Fig. 3 Changes on IVU during follow-up of 21 renal units (from a total of 160) that showed progressive scarring during follow-up. Classification of IVU is in accordance with the International Reflux Study Committee (1981). 0 = no scars. A = no more than 2 scars. B = more than 2 scars but areas of significant parenchymal thickness. C = diffuse thinness of parenchyma with generalised caliectasis. D = small kidney with insignificant parenchymal thickness. S = silent kidney.

Dwoskin and Perlmutter (1973) and Merrel and Mowad (1979) discussed the influence of reflux on growth. They both noted a marked retardation pre-operatively in both height and weight: for weight 11/35 (32%) were in the lowest twentieth percentile pre-operatively and only 2/35 (6%) post-operatively; for height the figures were 15/35 (42%) pre-operatively and 4/35 (11%) post-operatively. Dwoskin and Perlmutter (1973) reported figures for weight only and found 54% in the lowest quartile pre-operatively.

We found similar trends: weight was more retarded than height and after treatment, which was a combination of surgery and antibiotics, both growth figures tended to return to those found in the normal population. The question arises as to whether antibiotic therapy alone would have been as beneficial as the combination of surgery and antibiotic therapy. We cannot answer this question. However, in children with severe vesicoureteric reflux who were allocated randomly to either operative or non-operative treatment, the Birmingham Reflux Study Group (1987) found no significant difference between these groups in the incidence of breakthrough urinary infection, renal execretory function and concentration ability, renal growth, progression of existing renal scars or new scar formation. Reflux was abolished in 98% of ureters reimplanted, but more than half of the patients treated non-operatively continued to show severe reflux at 5 years. The preliminary results from our own institution showed that reflux grades 4 and 5 did not tend to be cured by antibiotic therapy alone (Scholtmeijer and Griffiths, 1988).

In cases of gross reflux, renal function is often damaged because of recurrent infection that causes scarring of the renal parenchyma. Lenaghan *et al.* (1976) reported abnormal kidneys at the time of diagnosis in 36% of patients and found that further deterioration could be prevented after reimplantation. Mundy *et al.* (1981) reported that in 10/73 children with initially impaired renal function, some degree of improvement occurred in terms of serum creatine and GFR. Antibacterial treatment also contributed to stabilisation of renal function (Steinhardt, 1985). In the reflux nephropathy study of Torres *et al.* (1980), further deterioration could not be prevented in 11/54 children.

Only 3 patients (3.8%) in the present series showed a rise in serum creatinine greater than would be expected from their ages. This is comparable with the findings of Skoog *et al.* (1987), who could find no significant alteration in renal function during surgical management of children with high grade reflux.

Hypertension is thought to occur in reflux nephropathy as a late complication.

Lenaghan *et al.* (1976) reported 10/102 cases with blood pressure over 140/90. In the study by Wallace *et al.* (1978) of a group of 116 patients, in which most children were over 10 years of age, 12.8% showed mild or severe hypertension. Scott *et al.* (1986) also believed that long-term follow-up was useful in detecting hypertension: they found hypertension in 14.3% of their patients: The International Reflux Study Committee (1981) concluded that hypertension could occur but felt that extensive renal scarring was not correlated with the appearance of hypertension. Other investigators found no hypertension in an 11-year survey of unilateral reflux (Quinlan and O'Donnell, 1985).

We were unable to confirm the development of serious hypertension in the present series.

In studies of reflux grades 1 to 3, renal scarring is seen in approximately 10 to 30%. In gross reflux an increase in the grade of scarring is seen in 30 to 50% of cases (Lenaghan *et al.*, 1976; Carpentier *et al.*, 1982; Bellinger, 1985; Steinhardt, 1985; Ozen and Whitaker, 1987; Skoog *et al.*, 1987). We found an incidence of 34% and progress in 19% of the children, representing 13% of the renal units. Most deterioration was seen in pre-operatively undamaged kidneys: 3/7 deteriorated by 2 or 3 grades. This progressive deterioration is in contrast to that reported by Skoog *et al.* (1987), who found progressive scarring on IVU in only 3/545 patients. Lenaghan *et al.* (1976) reported 21 to 66% progression, depending on the degree of initial scarring.

Most children with gross reflux presented in the first 3 years of life (55%) and 30% were under 1 year of age. In studies of less severe reflux (Carpentier *et al.*, 1982), very few children were younger than 1 year and the largest group was between 5 and 10 years of age. Thus gross reflux tends to present earlier, probably because of severe symptoms. This has been indicated by Ozen and Whitaker (1987), who found reflux grades 3 to 4 in children with a mean age of 2.9 years, while the mean age of children with reflux predominantly grades 1 to 2 was 5.6 years; in our series of reflux grades 4 and 5 the mean age was 3.5 years

We conclude that reimplantation in gross reflux is a safe and reliable procedure. The ultimate success rate of 96% and the prevention of further renal deterioration are comparable with the findings in studies of lower grades of reflux. Serum creatinine follow-up confirms this. The children are recovering well, as shown by the almost complete return of height and weight to normal values.

Some persistent renal damage was seen on IVU in 19% of the children. Progression was particularly evident in children with bilateral reflux, 27% of whom showed some renal deterioration; in children with unilateral reflux this was seen in only 15%. Most progression was by only 1 grade. Three patients deteriorated by 2 or 3 grades. The late development of serious hypertension was not seen.

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Circumcision—Which Dressing?

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Summary—Three methods of circumcision dressing were compared in a prospective trial. The results showed that dressings containing tincture of benzoin adversely affected wound healing in children. Dressing the wound with greasy tulle gave better results; the addition of soframycin did not produce better results than those achieved with ordinary paraffin tulle.

Circumcision remains the most commonly performed surgical procedure in the world. Usually the province of surgeons in training, it is performed in a variety of ways.

Some forms of dressing is usually applied post-operatively, but we know of no study comparing the various dressings in common use. Discomfort and poor healing following this operation are not unusual and we wished to see if there was any suggestion of local irritation adversely affecting the results. This prospective study did not attempt to establish whether dressings were beneficial but sought to identify if one form of application was superior to another.

Patients and Methods

The criteria for circumcision were as follows. Symptoms related to the foreskin such as persistent painful micturition with evidence of phimosis, or more than 2 episodes of balanoposthitis. Simple non-retracting prepuce under the age of 10 years without symptoms was not an indication for surgery. True phimosis after 10 years of age or balanitis xerotica obliterans were regarded as indications for surgery. Operation was performed by free hand technique and haemostasis secured with bipolar diathermy. Sutures were of 40 plain catgut.

Study 1

Two commonly used methods of post-circumcision dressing were compared, the first being wrapping with 0.5 inch ribbon gauze soaked in tincture of benzoin compound, and the second wrapping with soframycin impregnated tulle gras folded into a bandage. The patients were bathed daily at home after 24 h and parents were advised to let the dressings come away spontaneously. Patients were allocated to each group alternatively from the start of the study irrespective of age or reason for circumcision. All wounds were assessed 7 days later by one of us (N.L.).

Study 2

This assessed whether local antibiotic therapy in the dressing led to improved healing, and patients were allocated alternatively to a paraffin tulle or sofratulle dressing. The dressing was tied in place with 2 or 3 of the wound sutures which were then cut at 24 h, allowing the dressing to fall off. Bathing instructions were as before and patients were again assessed on the seventh post-operative day. An assessment was made according to the criteria in Table 1. Statistical analysis was carried out using the χ^2 test.

Results

Study 1

It was initially planned to have 100 patients in each group, but an interim assessment was made after

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Table 1 Grading Score for Wound Healing at 1 Week in Studies 1 and 2

	Grade
Raw moist areas on wound or glans	0
Dry scab on glans and wound	1
Healed, scabs on wound edge only	2
Healed, no scabbing or crusting	3

Table 2 Results of Grading Wound Healing at 1 week in Study 1

Grade	*Tincture of benzoin wrap (n=54)*	*Soframycin tulle wrap (n=54)*
0	41	28
1	5	4
2	7	14
3	1	8

54 cases. The study was then abandoned because the dressing was adversely affecting healing in the ticture of benzoin group (Table 2). (χ^2 test $P > 0.01$).

Study 2

The second study was undertaken with 105 cases in each group and it was found that the addition of antibiotic (soframycin) neither accelerated nor retarded the healing process (Table 3). (χ^2 test $P > 0.70$).

Discussion

The results demonstrated that healing by primary intention occurred in less than half of the patients within 7 days of surgery. It is the damage to the epithelium of the glans which is responsible for the delay in healing in children, related to the failure of separation of the glans from the inner layer of the foreskin.

Table 3 Results of Grading Wound Healing at 1 Week in Study 2

Grade	*Paraffin tulle (n=105)*	*Soframycin tulle (n=105)*
0	45	48
1	16	18
2	21	24
3	23	15

Any irritant, chemical or mechanical, is likely to delay healing of this particular part of the circumcision wound. We have no evidence that infection is responsible for delayed healing in any of these patients, and the addition of soframycin locally seems to confer no benefit.

Paraffin tulle seems to be beneficial when used as a circumcision dressing in children.

Although this report only addresses the question of which dressing to use, we are currently assessing whether a dressing is really necessary at all and this will be the subject of a further communication.

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Case Reports

Foreign Body in the Bladder

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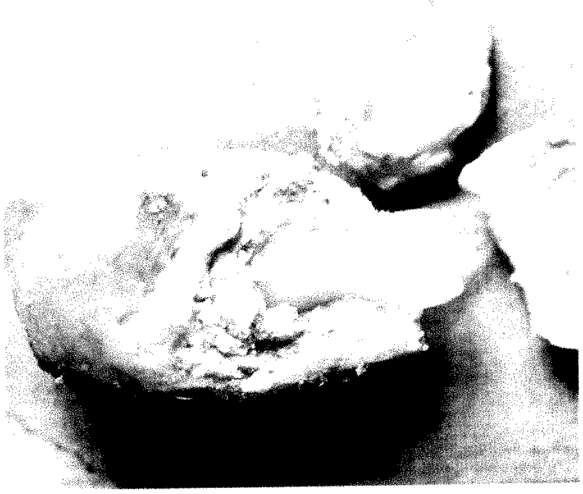
Case Report

A 32-year-old, male Egyptian presented to the Casualty Department with acute retention of urine. A KUB showed a radio-opaque shadow in the area of the bladder. The retention was relieved by catheterisation. The patient was admitted for further investigation and the shadow proved to be a stone in the bladder.

It was noted that there was an oblong filling defect in the heart of the stone. There was no past history of surgery to explain the presence of a foreign body inside the bladder. Cystolitholapaxy was carried out and examination of the stone revealed a large plastic bean, of the kind used for praying, within the stone (Fig.).

Comment

It is the practice in some areas of upper Egypt, from whence the patient came, to introduce threaded beans knotted at the end of plastic through the urethra up to the verumontanum for sexual pleasure, achieved by pulling the thread to mobilise the plastic bean inside the urethra. This patient was unlucky; the thread was cut and the foreign body remained in place for more than 7 years, forming the stone illustrated.



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Traumatic Neuroma of the Penis

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Case Report

A 58-year-old man with long-standing, diet-controlled diabetes, inadvertently walked through a plate-glass door in January 1985. He sustained lacerations to the face, hands, groin and to the shaft of the penis which were primarily sutured. The wounds healed well but several weeks later he developed a tender lump on the dorsolateral aspect of the penis, deep to the skin and slightly distant from the original wound. Xeroradiography was normal; clinically this was an area of Peyronie's disease, though the patient felt it was related to the accident. He also had 2 episodes of haematuria. IVU, urethrography and cystoscopy revealed no obvious source. The lump became increasingly troublesome and in 1987 surgical exploration revealed a localised fibrous lump, 1.0 × 1.5 cm, arising close to the fascia of the right corpus, dorso-laterally, 2 cm below the glans. Careful dissection of the lump in theatre revealed no glass particles. Histologically this was a classical traumatic neuroma (Fig.) consisting of innumerable small nerve fibres irregularly distributed in a fibroblastic stroma. The lesion had apparently developed from an adjacent nerve in the tunica albuginea, just superficial to the corpus cavernosum. He has made a full recovery.

Comment

We are unaware of any previous reports of a traumatic neuroma arising from the penis, although neurofibromas, neurilemmomas and malignant schwannomas have all been previously reported (Dehner and Smith, 1970). Neuromas may complicate surgical procedures such as amputation or cholecystectomy (Tancino *et al.*, 1985), but they are more common after accidental trauma of more exposed sites, *e.g.* the digits (Cieslak and Stoute, 1946). We report this case because although attention may be drawn to penile pathology following trauma (*cf.* testis), misdiagnosis of traumatic lesions as Peyronie's disease (*vide supra*) may result in inappropriate management.

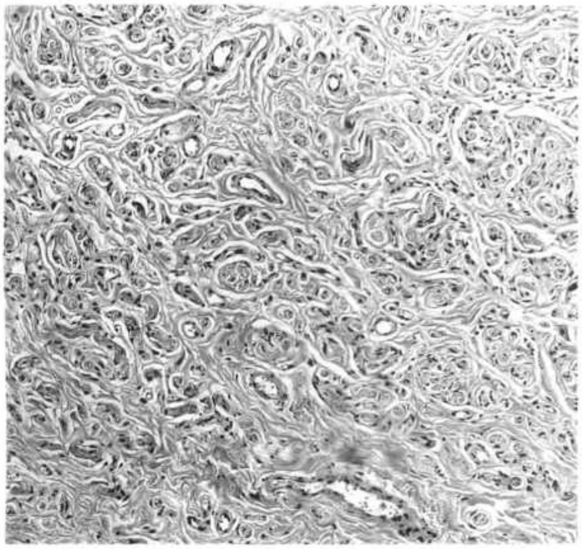

Fig. A classic traumatic neuroma (H and E × 100).

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Bilateral Ureteric Obstruction due to Endometriosis Resulting in Unilateral Loss of Renal Function

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Case Report

A 38-year-old woman was admitted with a 6-week history of increasing nausea, vomiting and bilateral loin pain. She had no genitourinary symptoms and systemic enquiry was unremarkable. In 1982 she had undergone a total abdominal hysterectomy for endometriosis, at which time it was presumed that all endometrial tissue had been cleared from her pelvis.

Physical examination was unremarkable and she was normotensive. Results of investigations on admission were as follows: urea 25.5 mmol/l, potassium 6.0 mmol/l, bicarbonate 19 mmol/l and haemoglobin 12 g/dl. An abdominal ultrasound demonstrated bilateral ureteric obstruction, worse on the right than the left, with a small atrophic kidney on the right.

The pelvicaliceal systems were decompressed using bilateral percutaneous nephrostomies. Following a short period of resuscitation her biochemistry returned to normal. She subsequently underwent cystoscopy and laparotomy. Cystoscopy revealed a normal bladder, but ascending ureterograms showed blockage 2 cm from the bladder on both sides. At laparotomy she was found to have a pelvis free of endometrial disease or adhesions, but the lower segments of both ureters were encased in dense fibrous tissue. Histologically, there was evidence of endometriosis in this fibrous tissue. Both ureters were reimplanted using Boari flaps. The patient made an uneventful recovery and was discharged 2 weeks later.

At follow-up, serial IVU and DPTA studies showed a very small and non-functioning right kidney, with a normal left kidney giving excellent overall renal function.

Comment

The incidence of obstructive uropathy secondary to endometriosis has been estimated at 1% (Docherty, 1944). The obstruction usually occurs at the level of the pelvic brim and may be due to endometriosis itself or more usually to secondary fibrosis. It has been reported that treatment with danazol can completely reverse the ureteric obstruction caused by endometriosis, but if secondary fibrosis has occurred, then surgical treatment may be necessary (Gardener and Whitaker, 1981).

In the present case it is instructive to note that by the time of definitive surgery one of the obstructed kidneys was so severely affected as to be essentially non-functioning. The present case raises the question as to whether patients with known pelvic endometriosis should have routine pre-operative and follow-up ultrasound or IVU examinations of their urinary tracts. If evidence of ureteric obstruction is demonstrated, then despite its well documented side effects, danazol should be used without delay before fibrosis and irreversible renal damage have occurred. If ureteric obstruction progresses, these patients may require early operative intervention.

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Detrusor Failure in Myasthenia Gravis

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Myasthenia gravis is an autoimmune disease caused by autoantibodies to acetylcholine (ACh) receptors which leads to neuromuscular blockade and hence weakness in a variety of muscle groups. The muscles of the face and limbs are most often affected. Only nicotinic receptors, and therefore only voluntary muscles, are thought to be involved in the disease process.

Case Report

A case of detrusor failure is reported in a female aged 59 years with a 35-year history of idiopathic non-familial myasthenia gravis responsive to pyridostigmine therapy. She complained of difficulty in voiding, a feeling of incomplete bladder emptying and urinary frequency; the symptoms were more pronounced when drug therapy was interrupted and were accompanied by generalised muscular weakness in such circumstances. Urodynamic studies were performed after discontinuation of pyridostigmine for 12 h. The bladder capacity was not reduced (430 ml) and there was normal bladder sensation during filling. However, during attempted voiding the patient was unable to accomplish a detrusor pressure greater than 8 cm of water and she voided by abdominal straining with poor flow rates and an interrupted flow pattern. Free flow rates performed in privacy demonstrated a similar low flow rate and interrupted flow characteristic of detrusor failure with compensatory voiding straining (Fig.).

Comment

Urinary symptoms have previously been reported in male patients with myasthenia gravis after prostatectomy (Greene *et al.*, 1974; Wise *et al.*, 1982). Incontinence in these cases was thought to be due to weakness of the striated distal urethral sphincter mechanism. The detrusor muscle is predominantly under the control of the parasympathetic nervous system and the cholinergic receptors of the bladder have not been shown to be involved in cases of myasthenia gravis. Detrusor failure is an unusual urodynamic finding which may occur as a result of diabetic neuropathy, chronic urinary retention or lower motor neurone pelvic nerve injury. In this case the disease process of myasthenia gravis appears to affect detrusor function and this could be due to autoantibody attachment to ACh receptors in the detrusor muscle itself or pelvic ganglia. No previous reports have suggested that drug-reversible detrusor weakness is a feature of myasthenia gravis.

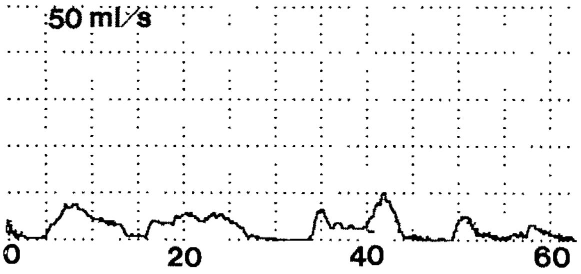

Fig. Free flow rate showing interrupted voiding pattern.

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Pilonidal Sinus of the Penis

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The term "pilonidal sinus" was first described by Hodges (1880) from the Latin "pilus"—hair and "nidus"—nest, and for many years was thought to affect only the region of the natal cleft. Nevertheless, examples of the condition in the hand, axilla, perineum, amputation stump, umbilicus and the suprapubic region have been described. We report a case affecting the penis which, to our knowledge, has not been described before.

Case Report

A 29-year-old, uncircumcised married man presented to the dermatologists complaining of an ulcer at the corona adjacent to the glans penis. He had first noticed a problem 7 months previously, when a small abscess appeared. This subsequently burst but failed to heal. A swab was taken by his family doctor and as this grew *Candida*

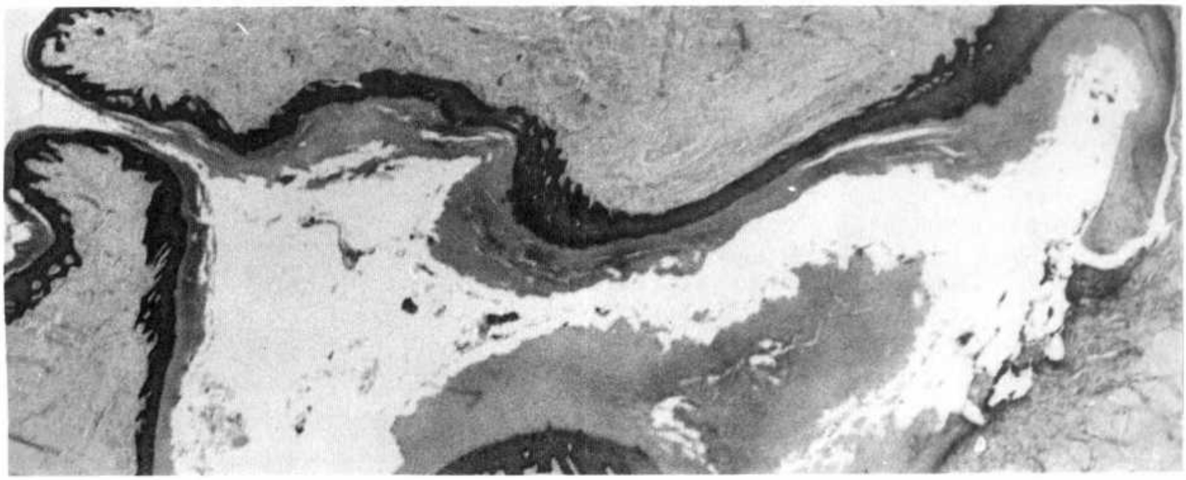

Fig. 1 Sinus tract lined by keratinising squamous epithelium and focally with inflamed granulation tissue. (× 2.5).

albicans and *Staphylococcus aureus*, treatment with miconazole and flucloxacillin was instituted. Persistence of a painless bleeding lesion at the base of the glans resulted in a surgical referral.

The patient was otherwise fit and well and on no medication. Examination revealed a 2 × 1.5 cm ulcerating lesion ventrally at the junction of the glans penis and the prepuce; it bled on contact and was infected. The lesion was indurated and there was a rolled edge to the ulcer. There was no lymphadenopathy. Venereal disease tests, TPHA, GCFT and chest X-ray were all negative and excisional biopsy was arranged under general anaesthesia. The lesion was excised completely and did not infiltrate deeply into the corpora cavernosa. Examination of the resected specimen showed a sinus track containing necrotic debris and hair (Fig. 1). Microscopy confirmed that the track was lined partly by necrotising squamous epithelium and partly by inflamed granulation tissue containing fragments of hair to which there were foci of foreign body giant cell reaction (Fig. 2).

The patient had an uneventful post-operative course and there was no recurrence of his symptoms 1 year after surgery.

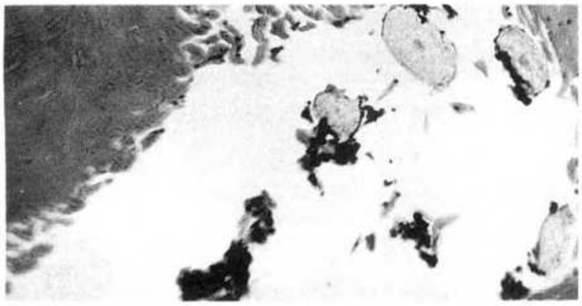

Fig. 2 Hair and debris present within the sinus cavity. (× 100).

Comment

Pilonidal sinus appears to be increasing in frequency (Goligher, 1984); it predominantly affects young dark haired males, is rare in negroes, but nevertheless does occur in blonde hairless types. The aetiology of the condition has remained controversial and a number of theories have been postulated to explain pilonidal sinus in the natal cleft. These are classified into congenital and acquired. Congenital theories implicate persistence of the medullary canal remnant and traction dermoid sinus formation; suggestions for possible acquired causes include implantation dermoid or simply that the hairs had been introduced into the tissues extrinsically (Goligher, 1984).

The support for the theory of extrinsic introduction came from their appearance in separate situations like the finger web (in barbers), the axilla and amputation stumps. Brearley (1955) postulated that the hairs burrowed into the skin by a process of twisting and drilling, finally losing their follicular attachments. Another explanation may simply be that the hair breaks off initially and then directly embeds into the skin.

The histological features classically show a sinus track from the skin-lined orifice extending into the subcutaneous tissues. Hairs are nearly always found projecting from the opening and may be attached to the wall of the track. In barbers, the hairs in the sinus are not the patients own hairs, and this may also apply in the case described. The principles of treatment for pilonidal sinus are simple excision with either primary suture or healing by wound granulation. In this case excisional biopsy and primary suture were performed for diagnostic and therapeutic reasons. This was the treatment of choice for the underlying condition, the wound healed well and the patient had no resultant disability.

We are not aware of any previous report of this condition in this situation and it adds further credence to the acquired theory of aetiology of this old, well recognised but poorly understood condition.

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Rectovesical Fistula due to Indwelling Catheter

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Case Report

An 80-year-old man was referred with a 2-week history of passing urine *per rectum*. He had had a transurethral resection of a benign prostate 4 years previously. Since then he had had an indwelling catheter for incontinence due to Parkinson's disease, senility and immobility. His catheter had been changed every 6 to 8 weeks.

On examination he had a moderately enlarged, clinically benign prostate. The anterior rectal wall above the prostate felt indurated and irregular. Sigmoidoscopy and a barium enema were both normal. Cystography confirmed the presence of a rectovesical fistula.

At laparotomy a short fistulous track was found to extend from bladder to rectum immediately inferior to the pelvic peritoneal reflection. On opening the bladder, the balloon of the indwelling catheter was found to lie in a trigonal crater, from the centre of which the fistula began. The crater was separated from a normal bladder neck by normal mucosa. Bladder and rectum were otherwise grossly normal. The fistula was resected and both bladder and rectum repaired. Histological examination of resected tissue showed chronic inflammatory change only.

Comment

Rectovesical fistulas account for approximately 20% of all enterovesical fistulas (Couris and Block, 1963; King *et al.*, 1982). Although trauma has been an infrequent cause of enterovesical fistula, traumatic cases have usually involved the rectum. Couris and Block (1963) found that 34 of 46 cases of traumatic rectovesical fistula were due to surgical trauma, usually complicating suprapubic and other forms of prostatectomy. The history and operative findings in this case were most suggestive of the fistula having been due to pressure necrosis by the balloon of the catheter. Although rare cases of rectovesical fistula have been attributed to trauma associated with foreign bodies, we have not found any reports implicating indwelling catheters.

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Spontaneous Thrombosis of the Penis in a 50-year-old Patient Fully Anticoagulated on Warfarin

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Case Report

A 50-year-old male developed painful engorgement of the penis 2 weeks after commencing oral anticoagulation for a pulmonary embolus. There was no history of trauma. On examination, complete penile thrombosis with a glandular erection was present despite over-anticoagulation (British Prothrombin Ratio 5.0). Warfarin was discontinued and intravenous anticoagulation commenced, requiring 17,000 units of heparin 6-hourly. A single dose of 100,000 units streptokinase was given peripherally and empirical prednisolone commenced.

Within 24 h significant improvement had occurred and by the end of 1 week complete resolution had taken place. A venogram was normal and computed tomography revealed no neoplastic cause for his coagulopathy. The clotting cascade was investigated by the haematologists but no diagnostic abnormalities were detected.

Comment

Complete spontaneous thrombosis of the penis has been described only in a bull (Hudson, 1971). Cases of partial thrombosis of the corpora cavernosa associated with trauma or congenital webs have been described (Becker and Mitchell, 1965). Reports of complete thrombosis of the penis have occurred in association with other pathology such as phlegmasia cerulea dolens and thrombosed inferior vena cava (Sodol *et al.*, 1978). No case of complete spontaneous thrombosis of the penis in the human has been described. In this case the prompt administration of the streptokinase prevented infarction and undoubtedly saved the penis.

No evidence of return of physiological function has occurred, but follow-up continues.

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Rotational Injury of the Penis

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Case Report

A 27-year-old male presented 12 h after injury with swelling and pain of the penis. During intercourse in the standing position, with his partner recumbent, she had attempted to rotate through 180°. He then experienced sudden pain in the penis with gradual detumescence. Physical examination revealed a generalised penile haematoma but no deformity.

Immediate surgical exploration via a subcoronal incision allowed the shaft to be degloved and the haematoma evacuated. No defect was detected in the tunica albuginea but the superficial dorsal vein of the penis was found to be completely divided. The vein was ligated. Post-operative follow-up at 4 weeks revealed no deformity and the patient had achieved successful intercourse.

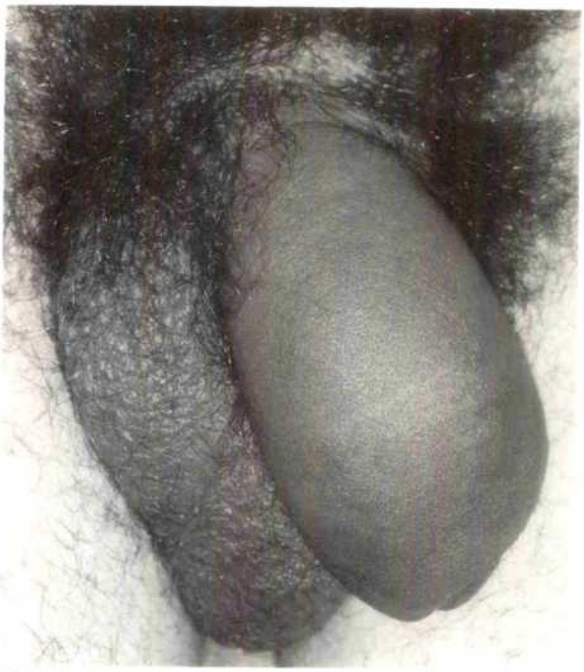

Fig. Penis 12 h after injury.

Comment

This is the first reported case of traumatic rupture of the superficial dorsal vein of the penis during intercourse. Although fracture of the penis seemed the most likely diagnosis, the absence of a cracking sound or immediate detumescence at the time of injury aroused some doubt.

Immediate surgical exploration of a fractured penis is preferential to conservative treatment (Ozen *et al.*, 1986) as it results in a lower incidence of deformity or painful erection. A subcoronal incision with penile degloving (Nesbitt, 1965) allows good exposure and full assessment of any injury.

Rupture of the superficial dorsal vein should be considered in the differential diagnosis of penile injury.

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Correspondence

Dear Sir,

re **Trial without catheter following acute retention of urine.** M. Taube and H. Gajraj. *Br. J. Urol.*, **63**, 180–182, 1989.

It would be appreciated if any events provocative of acute retention and the maximum flow rates had been analysed by the authors of this publication. Both of these factors are important predictors of preserved voiding ability (V. P. Klarsko *et al. Scand. J. Urol. Nephrol.*, **21**, 23–28, 1987). Patients with no provocative event had a risk 1.9 times higher for recurrent retention than patients with a provocative situation. The ability to produce a maximum flow rate less than 5 ml/s was associated with 75% recurrent retention. Thus the best patients for a catheter-free trial would be those with low residual urine, a provocative event and a maximum flow rate greater than 5 ml/s.

With regard to the timing of catheter removal, it appears that the authors may have removed the catheters too soon, but "little is known about the mechanism of retention in the male".

Prostatic infarcts were found in 85% of men with acute urinary retention and in 3% of men without retention of urine (L. H. Spiro *et al. Urology*, **3**, 345–347, 1974). With an infarct there is probably an increase in the size of the prostate due to oedema. Neurogenic disturbance may occur at the bladder neck secondary to anoxia from the presence of the infarct and may be a cause of retention. Hence one should give more time for this infarct-induced oedema to disappear.

Prolonged bladder distension in retention may of itself affect detrusor function either by bladder wall ischaemia or axonal degeneration, so that these detrusors cannot initiate a voiding contraction (K. Murray *et al. Br. J. Urol.*, **56**, 468–473, 1984). It is reasonable in such cases to wait for some time while the patient is treated by intermittent catheterisation until detrusor contractility is re-established before proceeding with prostatectomy (E. J. McGuire. Functional changes in prostatic obstruction. In *The Prostate*, ed. Blandy, J. P. and Lytton, B. P. 30. London: Butterworths). After relieving retention one does not know when the detrusor will be able to initiate voiding and urodynamics need to be done at regular intervals after relief of retention to appreciate the clinical implications of this interval. The cumulative risk of recurrent retention has been reported to be 56% after 1 week and 62% after 1 month (V. P. Klarsko *et al. Scand. J. Urol. Nephrol.*, **21**, 23–28, 1987), suggesting that the catheter should be left for at least 1 week.

In our experience, infection rarely troubles the patient with an indwelling catheter. The incidence of clinical bacteraemia and wound infections is no higher than in patients with no catheter and haemorrhage is not a problem in these cases.

From an organisational point of view there are considerable advantages in delaying admission by catheterisation. One may not only buy time to admit these patients but may increase the number of patients who do not require immediate prostatectomy.

Yours sincerely,

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Notices

British Association of Urological Surgeons

President: R. T. Turner-Warwick, DSc, DM, MCh, FRCP, FRCS, FACS

Annual Meeting: Scarborough. 10–13 July 1990

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Second Copenhagen Symposium on Uroradiology

Herlev, Denmark. 27–30 August 1990

The following topics will be included: Upper urinary tract imaging and intervention; Contrast medium nephrotoxicity; Hydronephrosis/obstruction; The urinary bladder; Genital radiology; The adrenal glands; Free communications.

International Continence Society: 20th Annual Meeting

Aarhus, Denmark. 12–15 September 1990

Further information from: Dr J. P. Nørgaard, Institute of Clinical Experimental Research, University of Aarhus, DK-8000 Aarhus C, Denmark.

Shackman Travelling Fellowship 1991

Applications are invited from Medical Practitioners registered in the United Kingdom who are Senior Registrars in an accredited training programme in urology or Consultant Urological Surgeons of no more than 5 years' duration. Applicants of equivalent university status will also be considered.

The Fellowships are intended to provide sufficient support to enable the holder to undertake a period of study, either in the United Kingdom or abroad, for a period of not less than 6 weeks.

The subject to be studied must be related either to urology or to renal transplantation and may be either a laboratory or a clinical investigation.

The closing date for applications is 1 September 1990.

Further particulars from and all correspondence to: Taylors, Solicitors, 119 High Street, Newmarket CB8 9AG.

British Journal of Urology (1990), 65, 428–429

Diary

1990

April 19–20 (SR)	**Andrology—A Two-day Symposium. Robin Brook Centre, St Bartholomew's Hospital, London. Contact Course Organisers (Mr R. S. Kirby or Mr W. F. Hendry), St Bartholomew's Hospital, West Smithfield, London EC1A 7BE. Tel: 01 601 8391.**
April 22–26	18th Biennial Congress of the Urological Association of South Africa. Durban, South Africa. Contact Uro 1990, P.O. Box 17008, Durban 4013, South Africa.
April 23–May 11	Block 2, Diploma Course. Institute of Urology, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.
April 27–28	Interactive Obstructive Uropathy. Manchester. Contact Mrs G. Trimble, Department of Urology, Withington Hospital, West Didsbury, Manchester M20 8LR
May 5–6	Athenian Days of Urology 1990. Athens, Greece. Contact Professor C. Dimopoulos, Department of Urology, Laiko Hospital, 115 27 Athens, Greece.
May 8–9	Seventh Basic Urodynamic Course. Watershead Conference Centre, Cannons Road, Bristol. Contact Mr. P. Abrams, Department of Urology, Southmead Hospital, Westbury-on Trym, Bristol BS10 5NB. Tel: 0272 505050, Ext. 3162.
May 10–11 (SR)	**Reconstructive Surgery. Two-day Course. Institute of Urology, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.**
May 13–17	**Annual Meeting of the American Urological Association, New Orleans. Contact The Secretary, AUA, 1120 N Charles Street, Baltimore, Maryland 21201, USA.**
May 20–24	European Nuclear Medicine Congress 1990. Amsterdam, The Netherlands. Contact QLT/Congrex, Keizersgracht 782, 1017 EC Amsterdam, The Netherlands.
May 27–June 3	Urological Society of Australasia. 43rd Annual Scientific Meeting Darwin–Kakadu. Contact ASM Secretariat, Urological Society of Australasia, 145 MacQuarie St, Sydney 2000, Australia. Tel: 27 4461
June 9–10	Société Belge d'Urologie: 55th Congress. Brussels, Belgium. The topic will be "Medical Films on Urology". Contact Dr F. F. Wart, C.H.U-I.M.C.A.G., Division of Urology, Boulevard Zoe Drion 1, B-6000 Charleroi, Belgium.
June 12	First Annual Meeting of the European Society of Paediatric Urology. Amsterdam, The Netherlands. The topic will be Posterior Urethral Valves. Contact Dr P. Mouriquand, "Le Dizenier", 11 impasse Mouillard, 69009 Lyon, France.
June 13–16	Ninth Congress of the European Association of Urology. Amsterdam. Contact QLT Convention Services, Keizersgracht 792, 1017 AC Amsterdam, The Netherlands. Tel: 010 31 20261372
June 18–22	Revision Course, Diploma in Urology. Institute of Urology, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.

June 24–28	Canadian Urological Association Meeting, Vancouver, British Columbia, Canada. (To be held jointly with members of BAUS). Contact Dr J. P. Collins, Ottawa Civic Hospital, 1053 Carling Avenue, Ottawa, Ontario K1Y 4E9, Canada.
July 10–13	BAUS Annual Meeting, Spa Conference Centre, Scarborough. Contact Secretariat, Royal College of Surgeons, Lincolns Inn Fields, London WC1. Tel: 01 405 1390
September 9–11	Biannual Conference of International Society for Dynamics of the Upper Urinary Tract. Stockholm, Sweden. Contact Anne-Charlotte Kinn, Department of Urology, St Gõrans Sjukhus, 112 81 Stockholm, Sweden.
October 4–5 (SR)	**Urological Management of Spinal Injury. Institute of Urology, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.**
October 16–19	25th Annual Meeting of the Egyptian Urological Association. Cairo, Egypt. Contact Dr Ahmad S. Bedair, 26 Adly Street, Flat 908, Cairo, Egypt.
October 17–19	Advanced Stone Management Course. Institute of Urology, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.
October 25–29	Second International Congress on "The Pelvic Floor"—Update Mangement. Fort de France, Martinique. Contact Bureau Congress: I.F.R.U.G. "The Pelvic Floor", 2 Square La Fontaine, 2, Paris 75016, France.
November 8–9 (SR)	**Renal Failure and Transplantation. Guy's Hospital, London. Contact Course Secretary, Institute of Urology, 172 Shaftesbury Avenue, London WC2H 8JE. Tel: 01 240 9115.**
1991	
January 22–25	Eighth Copenhagen Symposium on Endoscopic Urological Surgery. Herlev Hospital, Herlev, Denmark. Contact F. Rasmussen, Department of Urology, Herlev Hospital, 2730 Herlev, Denmark.
September 4–7	Twenty-first Congress of the International Continence Society. Budapest, Hungary. Contact A. Tankó, Üllõi ut 78/b, Department of Urology, Semmelweis Medical School, H-1082 Budapest, Hungary. Tel: (36) 1 1139 016.

Courses which are recommended for Senior Registrar Education are marked with (SR).

All 'BAUS–associated' meetings/courses are printed in bold.

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Book Reviews

Lasers in Urologic Surgery. Second edition. Edited by J. A. Smith, Jr., B. S. Stein and R. C. Benson, Jr. Pp. xxiv + 194. Chicago, London, Boca Raton: Year Book Medical Publishers. 1989. Price £50.50.

The second edition of this book, produced within 4 years, emphasises how rapidly this field is expanding. Five new chapters have been added to include sections on external genitalia, urethra, prostate and bladder, with much more detail of bladder cancer treatment and the place of the laser in both superficial and invasive disease. A very interesting section on percutaneous use of the laser in the upper urinary tract is followed by theoretical and practical discussions on laser lithotripsy. Contact laser surgery and "tissue welding" are welcome additions and the sections on practical laser safety and the organisation of a laser unit are now much more comprehensive. Photodynamic therapy, though still experimental, is reviewed in detail, showing both the drawbacks in the technique and possible future modifications.

The book is therefore, out of necessity, much larger than its predecessor and very well produced. Once again the illustrations are excellent. The authors are to be congratulated on a most up-to-date text.

Surgical Pathology of Prostate and Seminal Vesicles. By J. Kovi. Pp. 305. Boca Raton: CRC Press. 1989. Price: £85.00.

Until fairly recently, diagnostic histopathology textbooks in the field of surgical uropathology have been thin on the ground. Although the kidney has been comprehensively covered by a wide range of texts, including Heptinstall's 3-volume work, these have often been largely restricted to renal biopsy pathology, while for the remainder of the field, the AFIP fascicles and Pugh's *Pathology of the Testis* would probably be the main reference books in a British pathology department's library. More recently, a number of textbooks have covered the entire field of surgical urology, of which the best is Hill's 2-volume American textbook.

This book, as its title indicates, covers a much more limited field—that of the prostate—with a small section on the seminal vesicles. Prostatic pathology is covered comprehensively—256 pages, together with a short 10-page chapter on the seminal vesicles. Finally, there is a large bibliography of 827 references, with the most recent references being 1987.

Essential in any textbook aimed at the practising diagnostic histopathologist is that it is well illustrated, both in quantity (to provide a visual image of what the author is describing in words) and in quality. This book passes these tests with ease. The text is set out in a neat and concise manner with each one of the 19 chapters divided into sections and subsections. Nor surprisingly, half of the book is devoted to tumours of the prostate, but this reviewer found two of the most interesting to be on diagnostic immunohistochemistry of the prostate and atypical hyperplasia of the prostate.

Prostatic biopsies account for a small but significant proportion of the workload of most pathology departments. This book will remain a useful text for many years and its purchase by departments is recommended, although at £85 it is by no means cheap. Only individuals with a special interest in the prostate would consider personal purchase. This book will certainly be of value when diagnostic problems arise and it will also be a source of references.

Laser Lithotripsy. Clinical Use and Technical Aspects. Edited by R. Steiner. Pp. ix + 203. Berlin, Heidelberg, New York, London, Paris, Tokyo: Springer-Verlag. 1988. Price: DM112.-.

Laser lithotripsy is in its infancy, with the first commercial machines only just becoming available. This book presents papers given at the First International Symposium on Laser Lithotripsy. The authors of the papers are the pioneers of this new technology and have been attempting to establish the optimum conditions with which to achieve successful fragmentation of calculi of different chemical composition, whilst avoiding soft tissue injury. The papers report experience with a number of different lasers, different pulse durations, repetition rates, energy levels and transmission fibre configurations.

In the interest of speed of publication, the manuscripts have been photoset and this has the usual disadvantage of not allowing for any editing of the repetition of introductory prose, bad English and typographical errors. For the urologist who is hungry for information on this new and important method of stone fragmentation, there is plenty of information to be extracted from this book. It is not, however, an easy introduction to the subject for the casual reader or novice.

The Prostate. Edited by J. M. Fitzpatrick and R. J. Krane. Pp. xiv + 449. Edinburgh: Churchill Livingstone. 1989. Price £60.00.

This volume fills a gap in textbook coverage of prostatic disease since it addresses the prostate and its various diseases in general. From this point of view the subjects are wide ranging and well chosen and if one were wanting to acquire an overview of the prostate within the compass of one book, this is the book to buy. Each chapter provides an adequate coverage of its subject and goes into commendable detail in each case. Most are also well referenced and give abundant opportunity for further reading.

There is extensive coverage of benign prostatic hyperplasia in all of its aspects, including the history of the operation of prostatectomy and the various advances on the original open procedures. Controversial forms of treatment are also dealt with, such as local hyperthermia and cryosurgery.

The broad brush approach is similarly seen with carcinoma of the prostate. It was good to see a chapter on DNA flow cytometry and its potential application in prognosis and treatment; this is a line of investigation in which there is clearly much more to be done. The dilemma in treatment which continues, due to lack of an adequate number of controlled prospective and randomised studies, is manifest in the various chapters. The appearance of new markers and new modalities of diagnosis like prostatic ultrasound have yet to have an impact on this dilemma and are covered within the book. Prostate specific antigen was, however, dealt with somewhat summarily and it would have been helpful if more of its perspective could have been established within the chapter on diagnosis and methods of staging cancer. The radiotherapy of prostatic cancer, on the other hand, is well covered, as is radical retropubic prostatectomy and its place in treatment at the present time. The carefully described technique of the retropubic operation is supplemented by a much shorter chapter on the perineal approach which is ingeniously depicted in classic style using pencil sketches originally drawn by Elmer Belt. It is a pity that some of his script was not rendered a little more legible in the printing.

This book fulfils the intentions which the editors had at the outset in producing a book dealing with the basic anatomy and function of the prostate and leading on through its various diseases. It is very readable and will be enjoyed, as the editors hoped it would, by practitioners of all types and at all levels.

A Colour Atlas of Gynaecological Surgery. Volume 2—Abdominal Operations for Benign Conditions.

By D. H. Lees and A. Singer. Pp. 288. London: Wolfe Medical Publications. 1989. Price: £70.00

Surgical skill is commonly achieved by personal tuition complemented by textbooks with some drawings or photographs. This method has served generations of surgeons well but it has drawbacks. The 6 colour atlases of gynaecological surgery provide the ideal supplement to practical experience. They consist of step-wise instruction of most gynaecological procedures using a detailed series of excellent, life-size photographs with adjacent text and diagrams. The first editions have become a standard guide to gynaecological surgery in the United Kingdom and developing countries where access to postgraduate training is limited.

The revised volumes include more discussion on alternative techniques, such questions as prophylactic antibiotic use and the influence of pharmacological advances on surgery, *e.g.* endometriosis. There are more references and information on further reading. The 6 books concern vulval, vaginal and oncological surgery and operations related to infertility and pregnancy. Volume 2 tackles abdominal procedures for benign conditions such as hysterectomy, appendicectomy, laparoscopy and closure of pelvic fistulae. The authors stress the need for knowledge of basic principles before embarking on surgery but there are omissions which could have worrying consequences.

An early section stresses the vulnerability of the urinary tract during pelvic surgery, but defining the ureters is not mentioned in the hysterectomy text. Urinary damage occurs infrequently but abdominal hysterectomy is the commonest cause; there should, therefore, be advice about locating and protecting vital structures. Repair of vesico-vaginal fistula with ureteric and renal complications is described but there is no mention of the considerable expertise necessary and the need for a urologist's involvement. Without these the likely outcome is failure, dissatisfaction and litigation. Despite the reservations, the concept and execution of the volumes are excellent and the result is an immense achievement. They are required reading for all pelvic surgeons, from the trainee seeking to consolidate experience to the senior wishing to extend the repertoire.

Drugs, Systemic Diseases, and the Kidney.

(Advances in Experimental Medicine and Biology, Volume 252). Edited by A. Amerio, P. Coratelli, V. M. Campese and S. G. Massry. Pp. xii+405. New York, London: Plenum Press. 1989. Price: US$89.50.

This book consists of the collected papers from the Third Bari Seminar in Nephrology held in 1988. The contributions range from short reviews of major topics to more conventional clinical and experimental papers. This makes the pattern of the book uneven. The topics are wide ranging, reflect a number of individual enthusiasms and interests and are not in any sense comprehensive. There are some fascinating insights, such as the renal involvement in tuberous sclerosis and in Hantaan virus disease. Many of the papers are too brief to be of much interest and of course are not refereed and unlikely to appear in peer-reviewed journals. Some of the reviews are excellent, especially those on lupus nephritis (J. E. Balow), pre-eclampsia (J. M. Davison) and antihypertensive agents (V. M. Campese). It is clear that many of the papers relied on slides which are not reprinted here, so that their impact is lost. The references in the review articles are particularly good.

The volume is put together with a variety of typefaces and indifferent printing. The quality of reproduction of figures and tables is uneven and often poor. Most nephrologists will find something of interest in this book but it cannot be recommended to the majority of medical libraries.

Controversies and Innovations in Urological Surgery. (Clinical Practice in Urology Series). Edited by C. Gingell and P. Abrams. Pp. xvi+512. London, Berlin, Heidelberg, New York, Paris, Tokyo: Springer-Verlag. 1988. Price: £112.00.

This is the ninth book of the "Clinical Practice in Urology Series" and maintains the high standards set by previous productions. Messrs Gingell and Abrams have gathered an international group of experts to produce a book which provides an excellent review of innovations in the fields of stone disease, stress incontinence, neuropathic bladder, continent diversion, strictures, infertility and paediatrics. In other words, the book covers the sections of urology which are at the cutting edge of a rapidly developing specialty. Oncology is not included but it is covered by previous books in the series.

The book is beautifully produced, giving clear, well illustrated accounts of operative procedures and the rationale for such procedures.

Controversy arises from the juxtaposition of opposing views and this aspect is less obvious than the stimulating accounts of what is new in the specialty. This book constitutes essential reading for anyone with an interest in modern urology and whets the appetite for forthcoming titles in the series.

Urinary Calculi. ESWL, Endourology, and Medical Therapy. By J. E. Lingeman, L. H. Smith, J. R. Woods and D. M. Newman. Pp. xvi+460. Philadelphia, London: Lea and Febiger. 1989. Price £36.30.

This book provides a practical approach to the medical and surgical management of the urolithiasis patient. It is based on the experience of the Mayo Stone Clinic and the Methodist Hospital of Indiana, home of the first extracorporeal lithotriptor in the USA.

The first part of the book documents the history of stone surgery, the development of technology and the basic science of urinary stone formation. The second section is devoted to the medical and surgical evaluation of the patient with stone disease. The comprehensive chapter on medical evaluation is somewhat heavy reading, but serves as an excellent reminder that prevention rather than treatment is the ultimate goal. The third part discusses the specific management of non-staghorn, staghorn and ureteric calculi. There are interesting chapters on the bio-effects and the long-term results of ESWL. Surgical techniques are covered in the fourth section. This includes ureteroscopy, ESWL and percutaneous procedures and will be particularly helpful to urologists in training. The fifth part of the book concentrates on the economic and health policy implications of new stone technology, whereas the efficiency and cost of individual lithotriptors are compared in the final section. Useful information is provided for anyone involved in the organisation of a new lithotriptor service.

In summary, most urologists will find this book to be interesting reading. The authors' commitment to follow-up and their critical analysis of the various forms of treatment are admirable, allowing them to produce a definitive text on the mangement of stone disease.